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GUIDELINES

RSSDI Clinical Practice Recommendations for the Management of Type 2 Diabetes Mellitus 2022

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On behalf of RSSDI 2022 Consensus Group

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DIAGNOSIS AND CLASSIFICATION OF DIABETES

Recommendations

Recommended Care

Prediabetes/ intermediate hyperglycemia can be diagnosed with any of the following criteria:
- Impaired fasting glucose (IFG): FPG 110 mg/dL to 125 mg/dL or
- Impaired glucose tolerance (IGT): 2-h plasma glucose (2-h PG) during 75-g OGTT 140 mg/dL to 199 mg/dL or
- HbA1c ≥5.7%-6.4%

Diabetes can be diagnosed with any of the following criteria:
- FPG ≥126 mg/dL* or
- FPG ≥126 mg/dL and/or 2-h PG ≥200 mg/dL using 75-g OGTT
- HbA1c≥6.5% ** or
- Random plasma glucose ≥200 mg/dL in the presence of classic diabetes symptoms

Asymptomatic individuals with a single abnormal test should have the test repeated to confirm the diagnosis unless the result is unequivocally abnormal.
Individuals diagnosed with diabetes should be classified according to the World Health Organisation classification system.

Limited Care

Diabetes can be diagnosed with any of the following criteria:
- FPG ≥126 mg/dL* *or*
- FPG ≥126 mg/dL and/or 2-h plasma glucose ≥200 mg/dL using 75-g OGTT *or*
- Random plasma glucose ≥200 mg/dL in the presence of classic diabetes symptoms

Asymptomatic individuals with a single abnormal test should have the test repeated to confirm the diagnosis unless the result is unequivocally abnormal

The diagnosis of diabetes in pregnancy is dealt with in the **Chapter on Hyperglycaemia in Pregnancy**.

NOTE:
- Estimation of HbA1c should be performed using NGSP standardized method.
- Venous plasma is used for the estimation of glucose
- Plasma must be separated soon after collection because the blood glucose levels drop by 5%–8% hourly if whole blood is stored at room temperature.
- Capillary glucose estimation methods are not routinely recommended for diagnosis of diabetes/prediabetes/ intermediate hyperglycemia in the clinic setting; however, they may be used in epidemiological settings for assessing the population prevalence of diabetes and for individual diagnosis in resource-constrained environments where facilities for venous plasma glucose estimation are not immediately available. However, individuals detected to have dysglycemia using capillary blood glucose should have their diagnosis confirmed at the earliest by one of the methods mentioned above.[1]

For more details on glucose estimation, refer [2]

*FPG is defined as glucose estimated after no caloric intake for at least 8–12 hours.
**Using a method that is National Glycohemoglobin Standardization Program (NGSP) certified. For more on HbA1c and NGSP, please visit http://www.ngsp.org.

Background

The diagnostic criteria of diabetes have constantly been evolving. Both type 1 and type 2 diabetes mellitus are diagnosed based on the plasma glucose criteria, either the fasting plasma glucose (FPG) levels or the 2-h plasma post-load glucose (2-h PG) levels during a 75-g oral glucose tolerance test (OGTT), or the glycosylated hemoglobin (HbA1c) criteria which reflect the average plasma glucose concentration over the previous 8–12 weeks.[3] The International Expert Committee Report recommends a cut-point of ≥6.5% for HbA1c for diagnosing diabetes as an alternative to fasting plasma glucose (FPG≥7.0 mmol/L).[4]HbA1c testing has some substantial advantages over FPG and OGTT, such as convenience, pre-analytical stability, and fewer day-to-day fluctuations due to stress and illness. [4] Additionally, HbA1c has been recognized as a marker to assess secondary vascular complications due to metabolic derailments in susceptible individuals.[3,5,6]However, given ethnic differences in sensitivity and specificity of HbA1c, population-specific cut-offs might be necessary.[7,8]The high prevalence of iron deficiency anemia and (in specific geographies) hemoglobinopathies, and thalassemia in India may lead to over- or underdiagnosis of diabetes/prediabetes/ intermediate hyperglycemia when HbA1c is used as the sole diagnostic criterion.[9,10]Moreover, measuring HbA1c is expensive compared to FPG assessments. Standardization of measurement techniques and laboratories is poorly practiced across India.[11] Also, in several countries, including India, HbA1c demonstrated inadequate predictive accuracy in the diagnosis of diabetes; there is no consensus on an appropriate cut-off point of HbA1c for the diagnosis of diabetes in this high-risk population.[12] In view of this, the panel expressed concerns about using HbA1c as the sole criterion for the diagnosis of diabetes, particularly in resource-constrained settings. Therefore, a combination of HbA1cand FPG would improve the identification of individuals with diabetes mellitus and prediabetes/ intermediate hyperglycemia in limited resource settings like India.

Considerations

The decision to set diagnostic threshold values was based on the cost-effective strategies for diagnosing diabetes that was reviewed in the Indian context.

Rationale And Evidence

Glycosylated hemoglobin cut off for diagnosis of diabetes in Indian patients

• The RSSDI expert panel suggests

- HbA1c ≥6.5% as an optimal level for diagnosis of diabetes in Indian patients
- HbA1c cannot be used as the 'sole' measurement for the diagnosis of diabetes in Indian settings.
- However, the panel emphasized that HbA1c can be used in settings where an appropriate standardized method is available.

These recommendations are based on the following evidence:

• A recent study conducted on Singapore residents of Chinese, Malay, and Indian races to assess the performance of HbA1c as a screening test in Asian populations suggested that HbA1c is an appropriate alternative to FPG as a first-step screening test. A combination of HbA1c with a cut-off of ≥6.1% and FPG level ≥100 mg/dL would improve detection in patients with diabetes.[7]

• A study to assess the diagnostic accuracy and optimal HbA1c cut-offs for diabetes and prediabetes/ intermediate hyperglycemia among high-risk south Indians suggested that HbA1c ≥6.5% can be defined as a cut-off for diabetes and that HbA1c ≥5.9% is optimal for prediabetes/ intermediate hyperglycemia diagnosis and that a value <5.6% excludes prediabetes/ intermediate hyperglycemia/diabetes status.[11]

• Data from a community-based randomized cross-sectional study in urban Chandigarh suggest that the HbA1c cut point of 6.5% has optimal specificity of 88%. In comparison, the cut-off end of 7.0% has a sensitivity of 92% for the diagnosis of diabetes.[13]

• The results of the Chennai Urban Rural Epidemiology Study (CURES) demonstrated 88.0% sensitivity and 87.9% specificity for the detection of diabetes when the HbA1c cut-off point is 6.1% (based on 2-h post-load plasma glucose) and 93.3% sensitivity and 92.3% specificity when HbA1c cut off point is 6.4% (when diabetes was defined as FPG ≥7.0 mmol/l).[14]

Classification of Diabetes

The World Health Organisation[15] in 2019, revised the classification of diabetes to provide the best possible compromise between an etiological and clinical classification and to develop a classification system that is feasible to implement in different settings throughout the globe. This system divides diabetes into six broad subgroups (Table 1).

Table 1: Six groups of Diabetes according to the WHO

S. No	Category
1.	Type 1 diabetes (T1DM)
2.	Type 2 diabetes (T2DM)
3.	Hybrid forms of diabetes: - Slowly evolving immune-mediated diabetes in adults (previously termed LADA-latent autoimmune diabetes of adults) - Ketosis-prone T2DM (previously termed Flatbush diabetes)
4.	Other specific types - Monogenic diabetes (defects of beta-cell function or insulin action) - Diseases of the exocrine pancreas - Endocrinopathies - Drug- or chemical-induced diabetes - Infection-related diabetes - Uncommon forms of immune-mediated diabetes - Other genetic syndromes sometimes associated with diabetes
5.	Unclassified diabetes - A temporary category used when diabetes does not fit into any of the other categories
6.	Hyperglycemia first detected during pregnancy - Diabetes mellitus in pregnancy - Gestational diabetes mellitus Hyperglycaemia first detected during pregnancy

Another phenotype of diabetes, observed in 4 to 11% of T2DM in the Indian context, is lean type 2 diabetes[16]. They have inherent peculiarities in hepatic insulin metabolism and altered behavior of key enzymes involved in carbohydrate metabolism. They respond well to oral antidiabetic agents and present more with peripheral neuropathy, infections, and microvascular complications, while the macrovascular disease is rare. Lean T2DM is characterized by body mass index (BMI) below 19, no evidence of malnutrition, pancreatic autoimmune β cell or exocrine pancreatic disease, and good C-peptide levels[17] . Recently, another phenotype of lean diabetes has been described, characterized by low c-peptide, lower hepatic glucose output by deuterated glucose measurements, and total body fat lower than in T2DM[18]. More studies are needed to evaluate the pathophysiology of diabetes in these lean individuals.

T2DM encompasses a broad spectrum of varying insulin deficiency and resistance combinations. Recently,21, it has been suggested that there are different subtypes of T2DM based on the "clustering" of several phenotypic variables. Attempts[20] to identify similar subtypes of T2DM in the Indian population have led to the identification of four "clusters," two of which are identical to those identified in the Caucasian population and two of which are unique to India. These clusters are:

• Severe insulin-deficient diabetes (SIDD) (characterized by low BMI and waist circumference, poor C-peptide, and high HbA1c)

• Insulin-resistant obese diabetes (IROD) (Novel cluster) (High BMI and waist circumference, preserved C-peptide, and moderately elevated HbA1c)

• Combined insulin resistant and deficient diabetes (CIRDD) (Novel cluster) (Low or normal BMI and waist circumference, preserved C-peptide, high HbA1c and triglycerides)

• Mild age-related diabetes (MARD) (Older age at onset, good C-peptide, good HDL, lower HbA1c)

There is some evidence[21] to suggest that these "clusters" differ in the natural history of the disease, risk of complications, and response to treatment.

Implementation

Individuals should be educated on the advantages of early diagnosis and encouraged to participate in community screening programs for diagnosis.

PREVENTION (INCLUDING SCREENING AND EARLY DETECTION) AND REMISSION

Recommendations

Recommended Care

Screening and early detection

- The healthcare service provider should develop a program to identify people with undiagnosed diabetes.
- The program should be based on the available support from the healthcare system/service capable of effectively treating newly detected cases of diabetes.
- Opportunistic screening for undiagnosed diabetes and prediabetes is recommended. It should include:
  - Individuals presenting to healthcare settings for an unrelated illness
  - Family members of patients with diabetes
  - Antenatal care
  - Dental care
  - Overweight children and adolescents at the onset of puberty
- Wherever feasible, community screening may be done
- Detection programs are usually based on a two-step approach:
  - Step 1: Identify high-risk individuals using a non-invasive risk assessment questionnaire
  - Step 2: Glycemic measure in high-risk individuals here random capillary glucose between 140mg/dL and <200 mg/dL is detected, and OGTT should be performed.
- Universal screening and diagnosis of gestational diabetes mellitus shall be made to identify women at high risk of future diabetes and cardiovascular diseases (CVD).
- During the screening, people with high blood glucose need further diagnostic testing to confirm the diagnosis. In contrast, screen-negative for diabetes should be retested every 3 years, especially for high-risk patients.
- Paramedical personnel such as nurses or other trained workers should be included in any primary diabetes care team.

Prediabetes

- People who screen-positive for prediabetes (FPG=100-125 mg/dL or 2-h PG in the 75-g OGTT=140-199 mg/dL or HbA1c=5.7%-6.4%) should be intervened with appropriate lifestyle modification.
- Screened and treated for modifiable risk factors for CVD such as hypertension, dyslipidemia, smoking, and alcohol consumption.
- Screening strategies should be linked to the healthcare system with the capacity to provide advice on lifestyle modifications:
  - May be aligned with ongoing support national programs available at community health centers
  - Patients with IGT, IFG should be referred to these support programs.
- People with prediabetes should modify their lifestyle, including:
  - Attempts to lose 5%-10% of body weight if overweight or obese
  - Participate in physical activity (e. g., walking) for at least 1-h daily if overweight or obese and at least half an hour daily if weight is normal/controlled.
  - 6-8 hrs of sleep
- Healthy lifestyle measures, including diet and physical activity, are equally crucial for non-obese patients with prediabetes.
- People with prediabetes failing to achieve any benefit on lifestyle modifications after six months may be initiated on oral antidiabetic agents (OADs):
  - Metformin: In younger individuals with one or more additional risk factors for diabetes, if overweight/obese and having IFG + IGT or IFG + HbA1c >5.7%, the addition of metformin (500 mg, twice daily) is recommended.
  - Alternatively, if metformin is not tolerated, alpha-glucosidase inhibitors (AGIs) such as acarbose or voglibose may be initiated.
- Other pharmacological interventions with pioglitazone, orlistat, vitamin D, or bariatric surgery are not recommended.
- People with prediabetes should be educated on:
  - Weight management through optimal diet and physical activity
  - Stress management
  - Avoidance of alcohol and tobacco

Remission

Definition: Remission should be defined as a return of HbA_{1c} to <6.5% that occurs spontaneously or following an intervention and persists for at least three months without usual glucose-lowering pharmacotherapy.

- The patient's remission of diabetes can be documented if this is not due to complications, comorbid conditions, or concomitant therapy.
- In a setting where HbA_{1c} is an unreliable marker of chronic glycemic control, FPG or CGM values can be used for diagnosis. A FPG <126 mg/dL (<7.0 mmol/L) or eA1C <6.5% calculated from CGM values can be used as alternate criteria.
- Testing of HbA_{1c} to document a remission should be performed just before intervention and at least three months after initiation of the intervention and withdrawal of any glucose-lowering pharmacotherapy.
- In the case of continued use of glucose-lowering drugs for other non-glycemic indications, diabetes remission cannot be defined.
- Testing to determine long-term remission maintenance should be done yearly or more frequently if indicated.
- Testing for potential complications of diabetes should be continued as routinely recommended for a person with diabetes.
- Remission of diabetes should be defined in the context of type-2 diabetes only.

Surgical Remission

- Bariatric surgery remains one of the best options for the remission of diabetes.
- Bariatric surgery produces significantly more consistent long-term remission than lifestyle modifications and diet.
- Quantum weight loss correlates with long-term remission.
- RYG is the gold standard surgical procedure.
- Complications rates of surgery are meager, and long-term vitamin supplementation is required

Limited Care

- The principles for screening are recommended care.
- Diagnosis should be based on FPG or capillary plasma glucose if only point-of-care testing is available.
- Using FPG alone for diagnosis has limitations as it is less sensitive than 2-h OGTT in Indians.

Prediabetes

- The principles of detection and management of prediabetes are the same as recommended care.
- Linkages to the healthcare system with the capacity to provide advice on lifestyle modifications and alignment with ongoing support national programs available at community health centers where patients detected with prediabetes can be referred are critical.

Background

Conventionally, prevention is considered Primary, Secondary, and Tertiary. Recently, an additional category has been recognized, which is called 'Primordial.'

Primordial prevention is defined as 'existing at or from the beginning. It refers to efforts in early life (pre-pregnancy, pregnancy, and infancy) to reduce the risk of diabetes at a later age. It is expected to curtail the escalating epidemic of diabetes in future generations.

Primary prevention refers to the prevention of the onset of the disease by modifying the risk factors such as obesity and insulin resistance.
Secondary prevention refers to early diagnosis and treatment of the disease to prevent complications.

Tertiary prevention refers to limiting physical disability resulting from complications and the institution of rehabilitation measures.

In this section, we will be dealing with only primordial and primary prevention. Secondary and tertiary prevention will be handled in later sections.

Primordial prevention

Susceptibility to type 2 diabetes is usually considered to be 'genetic' (non-modifiable), and the disease is said to be 'precipitated' by lifestyle factors (unhealthy diet, inactivity, stress, etc.) [22] Primary prevention strategies include treating high-risk individuals (middle-aged or elderly prediabetic and obese) by improving lifestyle or with drugs [23]. Post-reproductive individuals are usually targeted, which does not benefit the offspring. As such, it is equivalent only to the treatment of early diabetes.

Indian Perspective

Recent research has revealed an additional 'non-genetic' susceptibility to type 2 diabetes which involves 'epigenetic' mechanisms and is therefore expected to be modifiable[24]. Epigenetic modifications are the basis of differentiation during intrauterine growth and development and are influenced by the intrauterine environment. These involve chemical alterations in DNA (methylation) without alteration in the base sequence of genes, histones (acetylation), or miRNA molecules, all of which influence gene expression. Thus, a substantial part of epigenetic susceptibility to diabetes (and other non-communicable diseases (NCDs) develops during intra-uterine and early life ('Programming'). Within the intrauterine period, the most crucial window is thought to be periconceptional (within a few days of conception) when the whole genome is demethylated and remethylated (epigenetic reprogramming). The intrauterine environment during this crucial window is a significant influence on the epigenetic landscape of the conceptus [25]. Significant influences on offspring's epigenetic susceptibility include maternal nutrition (both under- and over-nutrition of macro- and micro-nutrients), metabolism (especially diabetes), hormones, stress, environmental pollutants (including endocrine disruptors), etc. [26] Though most of the research has concentrated on maternal epigenetic transmission, recent evidence suggests that paternal influences could also be necessary [27].

Interest in the epigenetic programming of diabetes exploded after Prof David Barker published a series of papers showing that lower birth weight increased the risk of type 2 diabetes (thrifty phenotype hypothesis) [28]. This was contrary to the prevailing idea that fetal overnutrition in diabetic pregnancies was a risk factor for later diabetes (fuel-mediated teratogenesis hypothesis of Pedersen and Freinkel) [29]. It is clear that fetal undernutrition and overnutrition influence diabetes risk, albeit the contribution of the two varies in different populations. Interestingly, fetal undernutrition (protein and micronutrients) and overnutrition (of calories, carbohydrates, and lipids) can co-exist, as seen in pregnancies in rapidly transitioning societies and obese populations [30]. India is a notable example. It's the double capital of the world for the number of low birth weight babies and the burden of diabetes. Maternal undernutrition is common in many segments of society based on poverty, poor education, and gender bias, and gestational dysglycemia is not uncommon in these women. Urban and higher socio-economic status women suffer from increasing obesity and pregnancy hyperglycemia accompanied by micronutrient deficiencies due to poor knowledge of healthy nutrition, challenging lifestyle, and religious-cultural practices. In both these situations, the fetus is exposed to a double burden of malnutrition. Indian babies are the smallest in the world (mean birth weight ~2.8 kg) but have a 'thin-fat' body composition (lower lean mass and higher fat mass) compared to the heavier European babies [31]. This reflects risk factors for future cardio-metabolic disease in the cord blood (more elevated insulin and leptin, as well as lower adiponectin concentrations) [32]. This comparative thin-fat phenotype of Indian neonates persists in multi-generation migrant Indians [32] and continues in childhood [33], puberty, [34]and later life[35–37]. This reflects higher diabetes risk in Indians compared to European populations at a younger age and a lower body mass index.

Over the last three decades, many observational cohort studies in India have provided rich information on links between early life growth and later risk of diabetes. Lower birth weight [38,39], shorter length, and higher ponderal index [40] have been associated with later diabetes. Rapid childhood growth in low-birth-weight children is a decisive risk factor and embodies the double burden of malnutrition during the life course of an individual [38–41]. Only a few studies have investigated the role of maternal nutrition in these associations, notably the Pune Maternal Nutrition Study. It highlighted an association of maternal low Vit B12 and Vit D and higher folate status with later adiposity and insulin resistance in the offspring [42,43]. Young adults (18-year-old) in this study had an average BMI of 19 kg/m^2, but 30 % (40% in males, 20% in females) had prediabetes (ADA criteria) [44]. This was associated with shorter length, smaller head circumference at birth, and higher maternal fasting plasma glucose during pregnancy, albeit within the normal range. Fasting plasma glucose concentrations at 18y were also strongly predicted by more elevated fasting plasma glucose at 6 and 12 years of age, indicating that metabolic abnormalities arise in early life. Glucose intolerance was predominantly driven by lower beta-cell response to prevailing insulin resistance (lower disposition index). Higher fasting plasma glucose at 6,12, and 18 years of age predicted pregnancy hyperglycemia in females. In another follow-up in Pune, children born in diabetic pregnancies showed a high prevalence of diabetes (5%) and prediabetes (37%) at age [45]. All these findings point strongly towards a role for early life nutrition (both under- and overnutrition) as a significant 'programming' exposure for future risk of diabetes and provide a background for interventions to improve the health of future generations. This is the central theme of the evolving science of Developmental Origins of Health and Disease (DOHaD) [46].

Primordial prevention trials have already started in India. The first one is the Pune Rural Intervention in Young Adolescents (PRIYA) began in 2012. It supplemented vitamin B12 with or without multi-micronutrients to adolescents in the Pune Maternal Nutrition Study [47]. The intervention improved micronutrient exposure of the offspring before conception and during pregnancy. The offspring's growth and development have improved compared to their mothers. Cardiometabolic health will be tested during later childhood but neurocognitive assessment between 2-4 years of age showed a beneficial effect of vit B12 intervention on cognitive and language performance [48]. Participants in a neonatal Vitamin D supplementation trial are being followed-up in Delhi to study risk evolution for NCDs [49]. An extensive community-based pre-conceptional intervention (HELTI-Einstein) is happening in Mysore to improve nutrition, hygiene, and other aspects of maternal health to reduce obesity-adiposity risk in children [50].

The government of India has strengthened efforts to improve the health of children, adolescents, and pregnant women through a series of initiatives [51]. In addition to short-term improvement, these have the potential to influence the long-term risk of diabetes and other NCDs in future generations. A pregnancy with a female child has an even more exciting prospect. The female fetus has all the ova in its ovary by 20 weeks of gestation [52]. Improvement in the mother's health holds the promise of improving the health of at least the next two generations (a trans-generational rather than inter-generational benefit). Let's equip Abhimanyus of modern India to be better prepared to escape from the diabetes chakravyuha.

In summary, recent research has discovered a novel possibility of an adjustable epigenetic susceptibility to future diabetes. The most prominent window for epigenetic programming of diabetes is in the periconceptional period and covers pregnancy, lactation, and infancy (first 1000 days of life). Improving maternal health before, during, and after pregnancy has the potential to curtail the escalating epidemic of diabetes in India. These facts must be widely disseminated to all the stakeholders, not the least to the policymakers, caregivers, and the target population. The government of India's beneficial schemes has the potential to influence the health of future generations if executed efficiently. Primordial is the best.

Summary:

- Conventional ideas like primary prevention efforts in adults with prediabetes are tantamount equivalent of early diabetes. They mostly don't help future generations because they are carried out in post-reproductive individuals They can be classified as 'secondary prevention' or 'remission'. Long-term follow-up in the Diabetes Prevention Programme of

the USA has shown a lack of effect on all-cause and cardiovascular mortality and retinopathy.

- Primordial prevention refers to intergenerational and early life measures to reduce risk factors for diabetes (beta-cell dysfunction, adiposity etc.) and other non-communicable diseases (different organs and systems)
- The best window for primordial prevention is pre-conceptional when the parents don't know that pregnancy has occurred. Thus, improving the nutrition and health of the young before marriage and pregnancy is crucial. This is a societal and community-based effort, not a clinical intervention.
- Ancient Indian literature tells us the story of Abhimanyu, who learned *in utero* how to enter Chakravyuh while listening to Krishna's chat with Subhadra. This is the first documented example of the 'intrauterine programming' of the brain.

Primary prevention

Primary prevention is of utmost importance to reduce the number of new cases of diabetes[1]. It is estimated that in India, more than 53% of the population live with undiagnosed diabetes [53]. The ICMR–INDIAB population-based data reported the overall prevalence of diabetes and prediabetes in all 15 states of India to be 7.3% and 10.3%, respectively. Age, male gender, obesity, hypertension, and family history of diabetes were the risk factors for diabetes in urban and rural areas.[54] An epidemiological survey across varied geographical locations in Tamil Nadu showed a sharp increase in the prevalence of diabetes in 10 years (2006 -2016) [55]. In 2016, the prevalence rates were 21.9% in the city, 20.3% in a town, and 13.4% in peri-urban villages (PUV). The corresponding prevalence of prediabetes also increased significantly; 19%, 21% and 14.6% in the city, town and in the villages respectively. In addition to the increasing age and family history of diabetes, waist circumference was strongly associated with the increasing trend in the population [55]. Diabetes among children and adolescents are also on the rise which could be partly attributed to the rising rates of obesity and metabolic abnormalities [56]. The need of the hour is to develop pragmatic, cost effective strategies for screening and primary prevention and extend the benefits to the population at large to reduce substantial lifetime health costs by the society [57]. The landmark trials done in India have focused on lifestyle modification (LSM) as the primary tool in prevention of T2DM (refs). They are briefly discussed below:

- The Indian Diabetes Prevention Programme-1 (IDPP-1)[58] as a community based randomized controlled trial designed to study whether primary prevention of diabetes was feasible in Asian Indian population who were younger, leaner and more insulin resistant than the white populations. A 30-month follow-up showed that the relative risk reductions were similar with the three interventions; LSM (29%), metformin (26%) and LSM + metformin (28%) with no additional benefit or effectiveness in combining both LSM and metformin (Figure 1_Panel A)

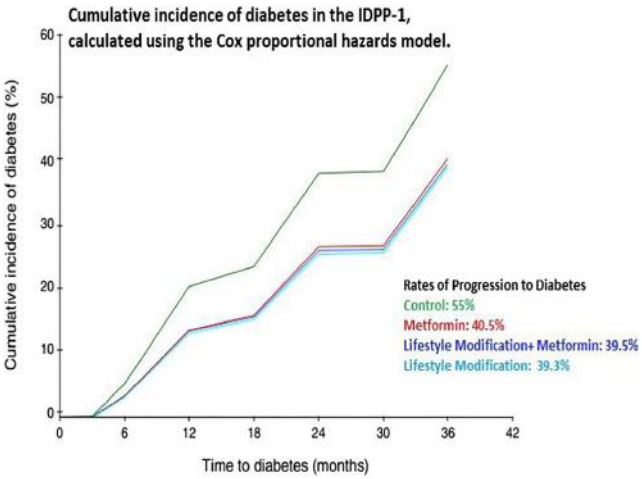


Figure 1_Panel A: Cumulative incidence of diabetes – results of the Cox proportional hazards model

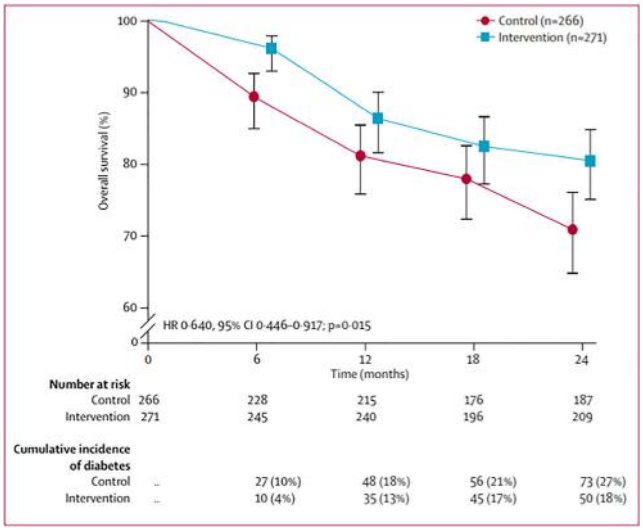


Figure 1_Panel B: The hazard ratio (HR) and survival curve for the intervention versus the control groups – results of the Cox regression analysis.

- The Indian SMS Study[59] was done to study the effectiveness of mobile phone messaging in preventing T2D in men in India. Persons with persistent IGT were randomized to the control and intervention groups. Control group received standard care advice only at baseline whereas the intervention group received standard care and motivational text messages through mobile phones at least three times a week. Six monthly reviews were conducted for a period of 2 years. The control group (n = 266) showed a 27% conversion to diabetes in 2 years and the intervention group (n = 271) showed a reduced rate of 18% (Figure 1_Panel B). Absolute risk reduction was 9% and the relative risk reduction compared to the control group was 36% which was highly significant. The number needed to treat to prevent one case of type 2 diabetes was 11 (95% CI 6–55).The reduction in the incidence was associated with improved dietary adherence which helped to increase the secretion of insulin and improvement in tissue insulin sensitivity. The study was the first to prove the effect of mobile technology or mobile health in primary prevention of diabetes
- The Diabetes Community Lifestyle Improvement Program (DCLIP)[60] was a randomized controlled trial among obese Indian adults with isolated IGT, isolated impaired fasting glucose (iIFG) or IFG + IGT. The control group received standard care advice and the intervention group received aggressive LSM training through once weekly classes regarding diet and exercise modeled on the basis of DPP study. In participants with no significant improvement in blood glucose during the initial 4 months, metformin 500 mg was added twice daily. During 3-year follow-up, 34.9% of control and 25.7% of intervention participants developed diabetes with a relative risk reduction of 32% (p = 0.014). A significant observation was that 72% required metformin in addition to lifestyle and the effectiveness was the least among iIFG.

Strategies have to be formulated considering the cultural, socio-economic aspects and structure of the health care system. Many long-term studies have proved primary prevention as the most potential and effective strategy to combat the rising epidemic of T2DM[56].

Considerations Relevant To The Development Of Screening Policy

The decision about conducting a screening programme should be based on the following factors:

Epidemiological considerations
• Clear evidence that screening is beneficial • High prevalence of undiagnosed type 2 diabetes • High prevalence of cardiovascular disease (CVD) risk and other complications amongst people with type 2 diabetes
Considerations of health system capacity
• High capacity of health care system for screening • High capacity of the health care system for effective clinical management of those who screen positive • High capacity of the health care system for supporting the psycho-social effects of screening • High capacity of the health care system to implement prevention strategies in individuals at high risk of the future development of diabetes even those who screen negative on that occasion
Economic consideration
• Low cost of early detection • Low cost of clinical detection

Adapted from Screening for Type 2 Diabetes - Report of a World Health Organization and International Diabetes Federation meeting [61]

Rationale And Evidence

Opportunistic screening

There are many challenges involved in identifying people at risk. The ideal approach to primary prevention would be the upstream strategy wherein the total population is targeted for prevention. This is not practical due to high cost, availability of healthcare personnel and other resources. Therefore, a high-risk approach (downstream strategy) is followed commonly. This approach was employed in the India prevention studies [62].

Risk assessment questionnaire

Scoring systems can be applied for selecting persons for screening with blood tests. Scoring (Risk Score) is based on non-invasive parameters such as age, family history of diabetes, body mass index (BMI), waist circumference, physical activity and hypertension. This strategy has become popular because it is non-invasive, least expensive and can be done on a large scale. In the Indian Diabetes Prevention Programmes a combination of risk score as the primary screening strategy, followed by a glucose tolerance test / HbA1c to identify people with prediabetes has been employed.

There are two risk scores specific for Asian Indians developed by Madras Diabetes Research Foundation [63] and by Ramachandran et al [64][Annexure 1 and 2]. These risk scores are validated and are being used widely in our country. Risk score assessment is simple and can be applied at any worksite by paramedical personnel to help identify high risk groups. Those at high-risk can be subjected to further blood testing.

Random plasma glucose level

Screening using random capillary blood (RBG) glucose offers great benefits for testing large numbers, at low cost and in a short time. A large community-based screening program in India studied the correlation of capillary RBG with oral glucose tolerance test (OGTT) values to define cut-points for identifying diabetes and prediabetes. It was suggested that a RBG value of >110 mg/dl (6.1 mmol/L) at screening can be recommended for definitive testing [65]. Also, a RBG cut point of 140 mg/dl (7.8 mmol/L) corresponded to the 2h PG ≥ 200mg/dl (11.1 mmol/L) used in diagnosis of diabetes [65]. A similar observation was reported by another large study also from the same city which derived a RBG cut-off value of 140.5 mg/dl (7.8 mmol/L) corresponding to an HbA1c value of 6.5% (48mmol/mol) (sensitivity 69%, specificity 83%, p<0.0001). The Area Under the Curve (AUC) was 0.823 ± SE 0.16 (95% CI 0.792-0.854). RBG showed significant correlation with HbA1c (r=0.40, p<0.0001) [66].

The panel endorse the IDF recommendation on the need to measure FPG and perform OGTT based on random plasma glucose levels which are associated with the development of diabetes (2-h PG ≥200 mg/ dL) or prediabetes (2-h PG ≥140 to <200 mg/dL)

Glycosylated hemoglobin (HbA1c) as criteria for screening

HbA_{1c} has evolved as a valuable tool for screening and diagnosis of diabetes and prediabetes and as a predictor of micro and macrovascular complications [67]. Assays of HbA_{1c} have multiple advantages over that of blood glucose including its preanalytical and analytical stability, its independence of the prandial status, and the assays are well standardized with high precision and accuracy. Presently the results are traceable to the Diabetes Control and Complications Trial (DCCT) assay values (measured as %) [68] and can also be compared to the highly accurate International Federation of Clinical Chemistry (IFCC)-standardized values (mmol/mol) [69]. High cost of the assay and its instrumentation, lack of awareness regarding its utility among the medical practitioners and the assay interferences (hematological abnormalities, hemoglobinopathies, and factors influencing erythropoiesis), limit its application. Healthcare professionals using the test should be aware of these limitations and use their discretion in interpreting the results.

Use of OGTT / blood glucose measure is a comparatively inexpensive, sensitive index of hyperglycemia including impaired glucose homeostasis. However, several disadvantages such as wide biological variability, poor reproducibility, influenced by acute factors such as stress, food, and exercise, and also by some medications, are the main disadvantages of using blood glucose [69].

In a recent study, Nanditha et al reported the concordance in the incidence of T2DM between cohorts with prediabetes, selected either by OGTT or HbA1c. Cumulative incidence of T2DM was similar at 12 and 24 months assessed using the respective diagnostic criteria (25.3% with glucose and 27.5% with HbA1c, p = 0.41 at 24 months). Both OGTT and HbA1c were found to have similar utility and validity in identifying persons with IGT [70] .

Intermediate Hyperglycemia Or Impaired Glucose Regulation (Prediabetes)

T2DM goes through several subclinical stages of abnormalities before its clinical manifestations occur. Prediabetes is typically defined as blood glucose levels above normal, but below diabetes thresholds and presented as either impaired fasting glucose (IFG) and / or impaired glucose tolerance (IGT). Nearly 20–30% of people with IGT will also have IFG; and about one-third of persons with IGT develop T2DM [15]. In India, the comparative prevalence (%) of IFG and IGT are 7.8% and 5.4 % respectively [53]. Recently, use of the term prediabetes has been criticized on the basis that not all people with this condition progress to T2DM and the term "intermediate hyperglycemia" is preferred.

Diagnosis of prediabetes or intermediate hyperglycemia

Impaired glucose tolerance is diagnosed when the 2-hour plasma glucose value after 75 gm glucose intake is between 140–199 mg/dL. The values for IFG are a fasting plasma glucose concentration of ≥110 mg/dL, but <126 mg/dL [15]. The ADA applies the same threshold for IGT, but uses a lower cut-off value for IFG (FPG of 100–125 mg/dL) [71]. The ADA has also introduced the use of HbA_{1c} levels of 5.7–6.4% (38.8–46.4 mmol/mol) as a new category of high diabetes risk.

Table 2: Diagnostic criteria for Prediabetes/ Intermediate hyperglycemia

	Fasting plasma glucose (mg/dL)	2-h plasma glucose (mg/dL)
Normal glucose tolerance (NGT)	<100*	<140
Impaired fasting glucose (IFG)	100–125	Non-diabetes <200
Isolated IFG	100–125	<140
Impaired glucose tolerance (IGT)	Non-diabetes <126	140–199
Isolated IGT	<100	140–199
Combined IFG/IGT	100–125	140–199

*The 100 mg/dL cut-off for IFG applies to guidance from the American Diabetes Association and the European Association for the Study of Diabetes/European Society of Cardiology; the lower cut off for

diagnosing IFG is 110 mg/dL according to the World Health Organization.

The American Diabetes Association (ADA) recommends diagnosing "prediabetes" with HbA1c values between 5.7–6.4%.

Pregnancy as a critical target for diabetes prevention strategies

Hyperglycemia in pregnancy that includes existing diabetes and gestational diabetes (GDM) enhances the risk of diabetes in the offspring. The increase in GDM poses challenges such as higher risk of diabetes among women and long-term consequences for the offspring. The offspring of mothers with GDM have increased risks of obesity, hypertension, diabetes, and other non-communicable diseases [72]. Given the high risk of GDM and the potential trans-generational effects, universal screening for GDM is necessitated.

Screening strategies for children and adolescents

Overweight (BMI >90 percentile) or obese children (BMI >99.5 percentile) with familial history of T2DM, and with associated risk factors such as insulin resistance, dyslipidemia, polycystic ovarian syndrome must be screened periodically.

Consistent with the recommendations for screening in adults, children at substantial risk for the development of T2DM should also be tested. The ADA recommends screening in overweight children and adolescents at onset of puberty. The screening must be performed every 2 years using fasting glucose or OGTT.

Rescreening

In a meta-analysis, investigators from multiple sites in India provided data regarding patients with T2DM aged ≤30 years. The data, although collected from tertiary care centers, showed a prevalence of T2DM ranging from 1.1% to 4.7% (average, 2.76%) in patients aged ≤30 years. It was also reported that 77.6 of these cases had a BMI of ≥23 kg/m^2 [73]. The expert panel therefore suggests that the general population should be evaluated for the risk of diabetes by their health care provider on an annual basis beginning at age 25 years. Annual or more frequent testing should be considered in individuals with a history of prediabetes or present with one or more risk factors that may predispose to development of diabetes. The panel opines that screening programs should be linked with the healthcare system.

Paramedical personnel

Paramedical personnel play a key role as facilitators in imparting basic self-management skills to patients with diabetes and those at risk. They can be actively involved in implementing diet and lifestyle changes, behavioral changes, weight management, pre-pregnancy counselling, and other preventive education. Nurses or other trained workers in primary care and hospital outpatient settings can help identification of individuals at risk of diabetes

Awareness Creation

Education and creation of diabetes awareness are the primary requirements to successful implementation of primary prevention in diabetes. Several programs have been taken-up by organizations in different parts of India; thePrevention, Awareness, Counselling and Evaluation (PACE) diabetes project, the Medical Education for Children/Adolescents for Realistic Prevention of Obesity and Diabetes and for Healthy AGing [MARG (The Path)], the media campaign for Prevention and Care of Diabetes (Jagran Pehel) Programme, Childrens' Health Education through Nutrition and Health Awareness (CHETNA)[62].

Implementation of the Program by Simple and Pragmatic Methods

For successful implementation of any program, major changes are required at personal, societal and community levels. Lifestyle intervention programs with the goals of decreasing excess weight, increasing physical activity, improving the quality of diet and refraining from unhealthy habits (smoking, alcohol, and stress) have proven to be effective in reducing diabetes risk in those with IGT.

Randomized Controlled Trials on Primary Prevention

Long term prevention trials conducted in multiethnic population including the US Diabetes Prevention Program (DPP), Finnish Diabetes Prevention Study (DPS), Chinese Da Qing Study and the Indian Diabetes Prevention Programme have shown that intervention with regulated diet, moderate physical activity or a combination of both results in significant risk reduction in the incidence of diabetes. Two Japanese trials have also shown the efficacy of LSM in primary prevention of T2D [62].

Sustained Effects of Prevention Strategies

Extended Post-trial Analyses

Extended trials such as the Chinese Da Qing study (CDQDPS), the Finnish Diabetes Prevention Study, the Diabetes Prevention Program Outcomes Study (DPPOS) in USA and the post-trial follow-up of the Indian SMS study have indicated that the benefits of LSM can last for periods varying from 3 to 23 years. The risk reduction in the LSM group was attributed to sustained adherence to the lifestyle changes [62] . The post-trial follow-up of the Indian SMS study investigated whether the beneficial effects of intervention persisted for an additional three years after withdrawal of active intervention for two years. The analysis showed that there was sustained reduction in incidence of diabetes after cessation of the intervention period. This indicated that many people continued to practice improved lifestyle even after cessation of the supervised prevention program [74].

Clinical Guidelines on the use of Metformin in Prediabetes

Evidence based studies showed that although metformin was less effective than lifestyle intervention, it was as effective as lifestyle intervention in certain groups of people. Participants who were young, those with a higher BMI, and women with a history of GDM were the most benefitted. Metformin promoted sustained weight loss and was associated with a significant reduction in the incidence of metabolic syndrome [75] .

Considering the effectiveness, safety, tolerability and minimal cost, metformin has been recommended by various expert groups such as the ADA and National Institute for Health and Care Excellence (NICE) for the therapeutic use for prediabetes alongside lifestyle modification. It is recommended for the young and obese, those with IFG, IGT or HbA1c levels between 5.7–6.4%. [56].

Table 3: Summary of recommendations on use of metformin for prevention of T2DM

	Summary of recommendations on use of metformin for prevention of T2DM
ADA	• To add metformin to lifestyle intervention especially for those with BMI ≥35 kg/m2, those aged <60 years, and women with prior GDM. • To monitor vitamin B12 periodically, especially where anaemia or peripheral neuropathy is present.
ESC/EASD	• Does not recommend pharmacological intervention in people with non-diabetic hyperglycemia. Recommends lifestyle changes to reduce the risk of new-onset diabetes and cardiovascular risk in subjects with "prediabetes" or non-diabetic hyperglycaemia.
NICE	• To apply clinical judgement on the use of metformin to (continued support for) lifestyle intervention for people with increasing HbA1c despite lifestyle intervention, or individuals unable to take-up intensive lifestyle intervention. • To consider metformin especially if BMI is ≥35 kg/m2. • To discuss potential risks and benefits and nature of treatment. • To try metformin for 6–12 months and discontinue if there is no improvement in glycaemia. • To monitor renal function initially and periodically (at least twice/per year).

Remission of Diabetes

Background And Evidence

Diabetes management continues to evolve. The last few decades have shown a paradigm shift in our understanding of prevention and remission of type-2 diabetes. There are many studies supporting the concept of diabetes remission including one of the earliest study from India by Ramachandran et al. in 1987[76]. Since then many definitions like "cure", "reversal", "resolved", "relapse" and "remission" have come up to define the condition.

The ADA international, multidisciplinary expert group with representatives from the American Diabetes Association, European Association for the Study of Diabetes, Diabetes UK, the Endocrine Society, and the Diabetes Surgery Summit have recently proposed that "Diabetes remission" is the most appropriate term [77]. It strikes an appropriate balance, noting that diabetes may not always be active and progressive yet implying that a notable improvement may not be permanent. An Indian expert group have proposed a comprehensive definition for remission of Type 2 diabetes as a "healthy clinical state" characterized by achievement of HBA1c below the targeted level, maintained for at least 6 months, with or without continued use of lifestyle modification and/or metformin, "provided that this is not due to complications, comorbid conditions or concomitant therapy"[78]. They have also proposed that the terminology of "remission of type 2 diabetes" should be clearly defined and used responsibly and sensibly[79]. The terminologies like "partial" and "complete" remission with Hba1c level below the diagnostic threshold for diabetes and below the diagnosis threshold of prediabetes respectively are more confusing and should be used with caution.

Glycosylated hemoglobin (HbA_{1c})below 6.5%, and remaining at that level for at least 3 months without continuation of the usual ant hyperglycemic agents as the main defining measurement. In case of continued use of glucose lowering drugs for other non-glycemic indications like use of metformin in PCOS, SGLT2 inhibitors in CKD or heart failure or use of GLP1 RA for obesity, diabetes remission can not be ascertained or defined[77].

HbA_{1c} measured must have a stringent quality control and standardization to international reference values [79–81]. In selected situations where the accuracy of HbA_{1c} values are uncertain or less predictable a FPG and /or CGM may be used to assess the correlation between mean glucose and HbA_{1c} and identify patterns outside the usual range of normal [82,83].

In the absence of HbA1c ,a FPG lower than 126 mg/dL (7.0 mmol/L) can be used as an alternate criterion for remission. This approach has the disadvantage of requiring fasting blood sample and sometimes significant variation in repeat measurements. Testing of 2-h plasma glucose following an OGTT is less desirable because of the complexity of doing the procedure and variability. In addition, bariatric surgery which is one method of achieving diabetes remission can alter the glycemic response to oral glucose .

Follow up strategy:

Testing of HbA_{1c} or another measure of glycemic control should be performed at least yearly. Routine follow up and measurements at 6 months and 12 months might be sufficient to identify remission and risk of relapse.

Even after a remission, the classic complications of diabetes both microvascular and macrovascula can still occur [84]. Hence, people in remission from diabetes should be advised to have regular retinal screening, tests of renal function, foot evaluation, and measurement of blood pressure and weight in addition to ongoing monitoring of HbA_{1c}.

Pathophysiology

Conventionally, type 2 diabetes is explained by increased insulin resistance and failure to meet the compensatory insulin demand by the beta-cells due to progressive apoptosis (1). Histological studies have shown that beta-cell number decreased by 24–65% in type 2 diabetes (2).

Contrary to this understanding, the *twin cycle hypothesis* has its basis on fat accumulation in the liver and pancreas being fundamental to the development of the disease (3). It is postulated that excess carbohydrate (from diet) undergo de novo lipogenesis, stimulated by insulin secretion which promotes fat accumulation in the liver. Individuals with relative insulin resistance in muscle accumulate hepatic fat more readily because of higher plasma insulin levels. Hepatic insulin resistance would bring about a tendency to increase plasma glucose levels resulting in compensatory elevation of fasting plasma insulin levels. A vicious cycle of hyperinsulinemia and blunted suppression of hepatic glucose production becomes established speeding the conversion of excess calories into fat producing very-low-density lipoprotein triglycerides (VLDL-TG). The export of VLDL-TG increase fat delivery to all tissues including the islets. The increased exposure to intra and ectopic fat by the pancreatic islets impairs acute insulin secretion in response to ingested food, and at a certain point, postprandial hyperglycaemia develop. Constant

hyperglycaemic status further increase insulin secretion rates, resulting in increased hepatic lipogenesis, spinning the liver cycle faster and driving on the pancreas cycle. The excess fat exposure causes beta cells to de-differentiate causing inability (downregulation of genes controlling insulin production) to secrete insulin leading to clinical onset of diabetes (3). The aetiology of the disease is therefore explained by hepatic insulin resistance and beta cell dysfunction rather than its deterioration which could be reversed by major calorie restriction and substantial weight loss especially in those who are obese or overweight. Interestingly, studies like the Indian Diabetes Prevention Programme from India have shown that the same mechanisms including improvement in insulin sensitivity could occur with lifestyle modification even in non-obese individuals, without clinically significant weight reduction (4). The chance of achieving remission through these strategies is largely determined by the beta cells to recover to its maximal capacity and function. Many studies have been conducted to provide the evidence base to this hypothesis (5-7).
Evidence Based studies:

A. Nutritional Basis

Dietary recommendations play a crucial role in remission of diabetes by aiding in weight loss. With relevance to modifying the existing dietary pattern, various strategies have been put forth; a low carbohydrate or calorie diet, restricted feeding time and improving dietary quality (8).
Studies in different populations have shown that both low calorie and low carbohydrate diets are effective for weight loss (9). In comparison to low fat diets, greater weight loss was achieved with low carbohydrate diets up to one year with a modest difference of around 1 kg body weight (10). Moreover, low or very low carbohydrate diets are preferred over fats as carbohydrates are the primary contributor to post-prandial glycaemia. In another study with intensive follow-up, sustained weight loss of 12 kg at two years was reported with a very low carbohydrate diet (11). Similarly, a study in UK, reported a decrease in median weight of 8.3 kg at a two year follow-up by using a low carbohydrate diet (50-130 g/day) (12).
The definition of a low carbohydrate diet varies widely across studies from <45% of total energy intake to ketogenic levels of <10%. (11,13). To avoid ambiguity, the following standard categorization is used (14).

- Very low carbohydrate: 20 to 50 g/day (≤10% of energy, based on 2000 kcal/ day)
- Low carbohydrate: >50 to <130 (>10% to<26%)
- Moderate carbohydrate: 130 to 230 (26%to 45%)
- High carbohydrate >230 (>45%)

Studies from India have also reported remission following a low calorie liquid diet (15). A cohort of young adults with recently diagnosed T2DM showed 75% remission at three months and 69% at two years; HbA1c was <5.7% in 53% of participants at three months and in 47% at two years; 22% had a value of 5.7-6.5% at both time points (16). A study from the Middle East observed remission in 61% of those allocated to total diet replacement and lifestyle intervention (17). In persons with prediabetes, remission at 6 months has been shown in an Indian cohort with significant improvements in insulin resistance and beta cell function by intensive lifestyle modification (4,18).
Traditional practices such as intermittent fasting, abstinence of food intake on certain days, time restricted feeding (eating within a 6 to 8 hour window each day) are effective strategies for weight loss by lowering the calorie intake by 25% (500 – 700 calories) (19). However, long-term studies are required to establish its effectiveness on remission. Moreover, reducing carbohydrates indiscriminately may lead to loss of consumption of fibre and wholegrain. Advice on foods consumed within theregular dietary pattern may facilitate better longer term adherence. Studies indicate that maintaining weight loss over 10 years without weight regain is feasible but requires sustained dietary change, regular physical activity and frequent self-weighing (20). Education, dietary guidelines and empowerment to make healthy food choices should be implemented at a population level.

B. Bariatric Surgery

Bariatric surgery has shown to reverse T2DM and change outcomes for obese patients for over 30 years[85] Reduction in post-prandial fatty acid intermediates (that inhibit glucose metabolism) following bariatric surgery result in utilisation of glucose or cellular fat storage. Remission of glycemia occurs even before weight loss after bariatric surgery implicating some hormonal mechanisms.
Bariatric surgery causes alterations in gastrointestinal hormone release, including ghrelin, leptin, cholecystokinin, peptide YY, and in particular, glucagon-like peptide 1 (GLP-1), which may correct feeding behaviour via the gut-brain axis in addition to sustaining euglycaemia. Studies have shown that postprandial levels of endogenous GLP-1 after bariatric surgery can be 10 to 20 times higher compared with before surgery. These hormonal changes occur in response to weight loss and depend upon type of surgical procedure. Interestingly, bariatric surgery causes dramatic changes in the gut microbiome, with reversion from an obesogenic profile to lean.
Systematic reviews showed that bariatric surgery could initially reverse T2DM for 58% to 95% of patients[86].The prospective Swedish Obese Subjects study reported remission rates of T2DM at 2, 10 and 15 years of follow-up as 72.3%, 38.1% and 30.4%, respectively[87].In a prospective Utah study of RYGB in class II obesity remission rate for diabetes were 75% and 62% at 2 and 6 years[88]. The Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) was a landmark study designed to examine the efficacy of bariatric surgery plus medical management compared to optimal medical management alone for glycaemic control among poorly controlled T2DM individuals. randomized in the RYGB, VSG and control arms in a 1:1:1 ratio. Remission rates were 42%, 27%, and 0% at year 1, 39%, 20%, 0% at 3 years and 22.4%, 14.9%, 0% at 5 years respectively for RYGB, VSG and conventional[89].
CROSSROADS trial[90] (Calorie Reduction Or Surgery: Seeking to Reduce Obesity And Diabetes Study) compared the effects of RYGB versus an intensive medical therapy combined with lifestyle intervention on T2DM remission (defined as HbA1c < 6% off antidiabetic medication), among individuals with T2DM and a baseline BMI ranging between 30 and 45 kg/m2. T2DM remission rates were 60% and 5.9% for the RYGB and non-surgical arms, respectively.
Another RCT by Courcoulas et al.[91] compared the effects of RYGB, AGB and non-surgical treatment on T2DM remission (as defined by the ADA) among individuals with T2DM and obesity grades I-II. The rates of partial and complete T2DM remission after 1 year of follow up were 50/17%, 27/25% and 0/0% for the RYGB, AGB and medically treated arms, respectively. After 3 years of follow up, remission (partial and complete) within the cohort was 40%, 29% and 0% for RYGB, AGB and the control group, respectively. In a meta-analysis of twenty-six studies in patients with BMI <30 [73] diabetes remission was reported in 43%.
The Second Diabetes Surgery Summit 2016 produced recommendations which were endorsed by 45 national medical societies worldwide, to use bariatric surgery as a treatment option for T2DM in adults with body mass index >40, or >35 kg/m2 in those with obesity-related co-morbidities. These guidelines were based on the observation that there was uniform improvement in glycaemic control after any bariatric operation [92].IFSO-APC Consensus statements 2011 suggest lower threshold i.e. BMI ≥ 35 with or without co-morbidities and BMI ≥ 30 with T2DM or metabolic syndrome for patients who are inadequately controlled by lifestyle alternations and medical treatment for acceptable Asian candidates for bariatric surgery.
The surgical approach may be considered as a non-primary alternative to treat inadequately controlled T2DM, or metabolic syndrome, for suitable Asian candidates with BMI ≥ 27.5. OSSI upholds the BMI criteria for bariatric and metabolic surgery of 2011 IFSO-APC guidelines. In addition waist circumference of ≥ 80 cm in females and ≥ 90 cm in males was added along with obesity related co-morbidities for surgery[93].
Not all individuals with T2DM experience remission after bariatric surgery. Unsurprisingly, the improvement of glycemic control relates to the

degree of weight loss after surgery, while less profound weight loss during the first postoperative year and greater weight regain may predict T2DM relapse. [76]

ABCD score (age, BMI, c-peptide, duration of diabetes) and DiaRem score models can predict remission of diabetes after surgery. Broadly long-term outcomes from bariatric surgery depend upon type of surgical procedure and patient baseline characteristics like weight, age, duration of diabetes and status of insulin secretory reserve (those already on insulin have low rate of remission). Gastric bypass which employs restrictive and malabsorption strategies is the most effective in inducing remission of diabetes followed by sleeve gastrectomy, and gastric banding.[94] 5 years long term data put remission rates for T2DM patients after sleeve gastrectomy as good as those for gastric bypass.[95] Other methods like laparoscopic gastric banding, gastric balloons and more recently "pill balloons" cause weight loss and remission of diabetes but long term data on diabetes is scant.[79]

There are complications involved with bariatric surgery. In clinical trials, mortality rate within one month and after was 0.08% and 0.31% respectively. Significant complications include anastomotic leak or haemorrhage, dumping syndrome, worsening acid reflux, marginal ulceration, and micronutrient deficiencies. For these reasons each patient risks from obesity and co-morbidities must be weighed up against the risks associated with bariatric surgery. [80]

Revisional surgery for recurrent metabolic disease has shown 65%-100% improvement of diabetes depending upon index surgery and subsequent reconstruction.

Revisional bariatric surgery has been shown to have utility for recurrent metabolic disease, especially T2DM. Depending on the index surgery and subsequent reconstruction, improvement of diabetes was seen in 65–100% of patients.

Further mechanistic research and much larger prospective randomized studies would be needed to identify the optimal treatment strategies for post-bariatric weight regain and relapse of T2DM with residual or recurrent metabolic disease.[87]

Pharmacotherapy

Most T2DM guidelines have focused on the pharmacological management of hyperglycemia, rather than weight loss, which was always a part of core management.[96] The increasing use of hyperphagic drugs like insulin and sulphonylureas was a further contradiction.

Logically thinking, pharmacotherapy alone cannot address underlying unhealthy lifestyles leading to overweight. Overweight/obesity is a chronic problem strongly driven by genetic factors with a high risk of relapse, and in addition . obesogenic addictive environment. T2DM is usually a progressive disease and current therapies are glucocentric not addressing the problem of visceral fat. Perhaps, the most depressing data by Kaiser Permanente study that found only a 0.23% remission rate with best practice standard care.[97]

In fact, the feasibility of reversing T2DM with pharmacotherapy has been demonstrated in numerous studies and with different medications. Studies have shown that, when implemented early in the course of T2DM (ideally less than 2 years), intensive insulin therapy for 2–3 weeks can induce a glycemic remission. In a meta-analysis, short-term intensive insulin therapy was found to significantly improve islet function and induce remission in 46% of patients at 12 months, and 42% at 24 months. This effect is weight-loss independent, without diet restrictions. Beta-cell re-differentiation was considered the important underlying mechanism for the treatment effect.

Jennings et al[98] found a triple therapy of metformin, pioglitazone and repaglinide to be effective for reversing newly diagnosed T2DM patients. The drugs were given at maximum tolerated doses and then tapered according to results.

Anti-obesity drug orlistat, a peripheral lipase inhibitor and a calorie restriction mimetic (CRM), has shown potential to improve glycemic parameters. Orlistat could be considered a type of drug that otherwise mimics the mechanism of action, effects, and long-term outcome noted with calorie restriction, without actually causing calorie restriction or lack of food intake.

High dose GLP-1 analogues (semaglutide) GLP-1/GIP dual analogues (tirzepatide) have been effective in controlling hyperglycemia and in decreasing weight. Their role in remission of diabetes is yet to be tested.

MEDICAL NUTRITION THERAPY (MNT) AND LIFESTYLE MODIFICATION

Recommendation

Recommended Care
MNT • The nutrition chart and support should be made by a trained nutritionist and a physician/diabetologist. • It should be based on TAF- Type, Amount, and Frequency
Carbohydrates • Carbohydrate content should be limited to 50%-60% of total calorie intake. • Complex carbohydrates should be preferred over refined products. • The low glycaemic index (GI) and low glycaemic load (GL) foods should be chosen. • The quantity of rice (GI: 73) should be limited as it has high GI; Brown rice (GI: 68) should be preferred over white rice. (Millets are another alternative) • Fiber intake: 25-40 gm per day.
Proteins • Protein intake should be maintained at about 15% of the total calories. The quantities of protein intake depend on age, sarcopenia, and renal dysfunction. • Non-vegetarian foods are sources of high-quality protein. However, intake of red meat should be avoided.
Fats • Fat intake should be limited (<30% of total calorie intake), with most sources being from nuts and seeds. • Oils with high mono unsaturated fatty acid (MUFA) and polyunsaturated fatty acid (PUFA) should be used. • Use of 2 or more vegetable oils is recommended in rotation. • For non-vegetarians, 100-200 g of fish/week is advised as a good source of PUFA, and for vegetarians, vegetable oils (soybean/ safflower/sunflower), walnuts, and flaxseeds are recommended. (Peanut oil and mustard oils are suitable based on their fatty acid composition) • Avoid consuming foods high in saturated fat (butter, coconut oil, margarine, and

ghee).
- Saturated fatty acids (SFAs) intake should be less than 10% of total calories/day (<7% for individuals having high triglycerides).
- Use of partially hydrogenated vegetable oils (Vanaspati) as the cooking medium should be avoided.
- Reheating and refrying of cooking oils should be avoided.

Food groups and patterns
- A diet rich in fruits, leafy vegetables, nuts, fiber, whole grains, and unsaturated fat is preferred. The plate should include pulses, legumes, unprocessed vegetables, and low-fat dairy.
- Portion size
  - Food plate should have vegetables and fruits as the main constituent (50%), both raw and cooked with a variety of vegetables over the week, adding diversity of vegetarian foods to increase intake of phytonutrients
- Extreme diets, including low-carbohydrate ketogenic, must be planned and executed following consultation with a physician and nutritionist and for a short period.
- Overall salt consumption should be <5 g/day (with sodium consumption <2300 mg/day).
- Avoid or decrease alcohol intake.
- Smoking cessation should be advised to all. Smoking cessation therapies may be provided under observation for patients who wish to quit in a step-wise manner
- Sugar-sweetened beverages are best avoided.
- Artificial sweeteners should be avoided as they alter the diversity of the gut microbiome and can increase insulin resistance.
- Meal plans with strategic meal replacements (partial or complete) may be an option under supervision when feasible.
- Indian fast foods-Street foods like kachori and samosa should be avoided.
- The advocation of fiber-rich fermented food.

Lifestyle modifications
- Physicians and diabetes educators could impart recommended care.
- Careful instructions should be given for initiating the exercise program. Help from a trained exercise therapist can be taken.
- Lifestyle advice should be given to all people with T2DM at diagnosis. It should be an effective option for controlling diabetes and increasing CV fitness at all ages and stages of diabetes.
- Lifestyle intervention is a cost-effective approach to the prevention of T2DM.
- Lifestyle interventions should be reviewed yearly or at the time of any treatment or every visit.
- Advise people with T2DM that lifestyle modification, by changing eating patterns like early dinners and physical activity patterns, can effectively manage several adverse risk factors related to T2DM.
- Physical activity should be introduced gradually, based on the patient's willingness and ability, and the intensity of the training should be individualized to the specific goals.
- The advocation of FITTE- Frequency, Intensity, time, training, Enjoyment
- A minimum of 150 min/week of physical activity is recommended for healthy Indians, given the high predisposition to develop T2DM and CAD, with the advocation of 60mins of exercise would be beneficial.
  - ≥30 min of moderate-intensity aerobic activity each day, including swimming, cycling, walking, or rowing.
  - 15-30 min of work-related activity
  - 15 min of muscle-strengthening exercises (at least three times/week), which can include lifting weights, working with resistance bands, inclined walking, sitting ups, or squats.
  - STEPS- At least 5000 steps per day.
  - Use of apps or Talk tests for assessment of the intensity of exercise.
- While the effect of yogic practices is encouraging, it should not replace aerobic exercise.
- Exercise advice should be modified in case of complications like neuropathy, retinopathy, and peripheral vascular disease. However, some appropriate exercise should be encouraged in these patients.
- Use of monitoring tools like accelerometers, GPS units, pedometers, mobile-based apps, or devices to measure the intensity and duration of physical activity may be encouraged.

Behavioral lifestyle intervention (BLI) / Behavioral Counseling
- BLI involves patient counseling for strategies such as tailoring goals, self-monitoring, and stimulus control.
- BLI approaches have been shown to improve adherence to lifestyle changes and achieve more sustained effects.
- Diabetes self-management support is essential and could be done with a physician or educator in small groups or face-to-face discussions in chat rooms.

Best Avoided
- Tobacco, Smoking, Alcohol
- Deep-fried, salted street foods
- Night munching and Late dinners
- Stress and unhealthy lifestyle

Limited Care
- Nutritional counseling may be provided by health care providers (HCPs) trained in nutrition therapy, not necessarily by an accredited dietician nutritionist.
- Overall, reduced consumption of simple carbohydrates, sugar, and fried foods and higher consumption of complex carbohydrates with high protein intake are recommended.
- Salt intake should be in moderation.
- Encourage increased duration and frequency of physical activity (where needed based on comorbidities and physical status complications.
- Mass awareness campaigns for a healthy diet and lifestyle should be conducted.

Background

An unhealthy diet and a sedentary lifestyle have been identified as modifiable risk factors in T2DM. Rapid urbanization and westernization with rampant availability of fast foods and processed foods that contain high amounts of refined carbohydrates, saturated fats, added sugars, and low fiber has dramatically changed the local food environment in India.[99] Along with increasing physical inactivity, these adverse dietary changes have been associated with detrimental influences on the onset and progression of T2DM in India.[100–102] MNT is a systematic approach to optimizing dietary intake to achieve metabolic control and maximize favorable treatment outcomes in T2DM. Conceptually, MNT involves counseling and recommendations from a registered dietician (RD) under the regular supervision of consulting diabetologists.

Current global clinical practice guidelines for T2DM from the ADA, American Association of Clinical Endocrinologists (AACE), and IDF advocate the importance of integrating MNT in the management of T2DM as first-

line therapy and provide consistent recommendations for day-to-day nutritional requirements.[103,104] MNT is a lifestyle transforming process beyond calorie restriction and portion control. Implementation of MNT in India is challenging owing to its cultural and culinary diversity. Consumption of high amounts of carbohydrates, including ghee-laden sweets loaded with sugar or jaggery, is inherent to the standard Indian diet and closely linked to cultural and religious traditions. Thus escalating the challenges of restricting carbohydrate intake. Therefore, designing individualized diet plans as a part of MNT in India should consider regional, cultural, economic, and agricultural factors, as all these have a marked influence on the acceptance of MNT by the patient.

Role of medical nutrition therapy in prevention and management

Dietary counseling, adherence to a healthful, calorie-restricted diet, and regular exercise have lower rates of incident diabetes in Indian men with impaired glucose tolerance. Community health programs and implementation of MNT-based model meals in rural and urban populations in South and North India have shown favorable changes in dietary patterns and parameters, including BMI, waist circumference, fasting blood glucose, and so on.[105–107] A stepwise Diabetes Prevention Program lowered the 3-year risk of diabetes by 32% (95% CI: 7, 50) in obese Asian Indian adults with any form of prediabetes.[108] These studies, including a few others involving Indians with risk factors for diabetes, reported benefits of dietary approaches such as high consumption of fiber-rich foods, high-protein meal replacements, or replacement of polished white rice with whole grain brown rice, and increased intake of fruits and vegetables.[109,110]

The prescription for diet should be given in the form of TAF: type, amount, and frequency of foods.

The landmark lifestyle intervention program, "Look Ahead," examined the effects of a calorie-restricted diet and reduced intake of high-GI carbohydrates such as sugar, flavored beverages, and high-calorie snacks on glycemic control and prevention of CV complications. At 11 years, participants benefited from the controlled diet. They had an average weight loss of 5% and substantial improvements in HbA1c levels, blood pressure, lipid profile, and overall fitness and well-being.[111] In a year-long prospective study from India, individuals with T2DM, randomized to MNT, achieved a significant lowering of HbA1c and all lipid parameters, especially triglyceride levels. This study involved 20 dieticians and reported the success of a guided, evidence-based, individualized MNT versus usual diabetes care.[112] Based on these clinically relevant observations in the Indian population, the RSSDI recommends the adoption of dietician-guided MNT as an integral component of diabetes management. The MNT and lifestyle modifications should be individualized based on disease profile, age, sociocultural factors, economic status, and the presence of sarcopenia and organ dysfunction.

Rationale And Evidence

Carbohydrate monitoring

Meal planning approaches should include carbohydrate counting, exchanges, or experience-based estimation and measurement of GI and GL to monitor the number of carbohydrates in food and understand the physiological effects of high-carbohydrate diets.[113,114]

High-carbohydrate, low-fat diets

Although there is a dichotomy in recommendations concerning high-or low-carbohydrate diets, historical data from India suggest the metabolic benefits of high-carbohydrate, high-fiber, low-fat diets as opposed to a high-fat, low-carbohydrate diet.[115,116]

Recommendation for MNT in patients with T2DM

MNT: Medical nutrition therapy; T2DM

In patients with Type 2 diabetes mellitus, high carbohydrate, high-fiber, low fat diets are recommended as opposed to a high-fat, low carbohydrate diet.[115,116] Recent studies support the implementation of a long-term high-carbohydrate, high-fiber diet in promoting weight loss, improving glycemic control, and lowering CV risk.[117–120] High carbohydrate diets should comprise significant amounts of unrefined carbohydrates and fiber such as legumes, whole grains, unprocessed vegetables, and fruits.[100,121,122] High carbohydrate diet regimens in T2DM patients have been associated with favorable weight loss and reductions in plasma glucose, HbA1c, and LDL levels with good adherence and sustainability, comparable with low carbohydrate diets. The concern of the possible untoward effect of a high carbohydrate diet on the lipid profile (increase in triglycerides and reductions in HDL) and CV risk can be mitigated by lowering the glycemic index of diets incorporating fiber-rich foods.[114]

Cross-sectional data from the CURES suggests that Indians consume high amounts of refined grains (~47% of total calories), which is associated with significant increases in waist circumference ($p<0.0001$), systolic blood pressure ($p<0.0001$), diastolic blood pressure ($p=0.03$), fasting blood glucose ($p=0.007$), serum triglyceride ($p<0.0001$), lower HDL ($p<0.0001$), and insulin resistance ($p<0.001$). Further, Indians who consumed refined grains were more predisposed to develop the metabolic syndrome (odds ratio [OR]: 7.83; 95% confidence interval [CI]: 4.72, 12.99) and insulin resistance versus those who consumed lower quantities.[123]

In an assessment of the quality and type of carbohydrates in a subset of patients from the CURES study, consumption of refined grain (OR: 5.31; 95% CI: 2.98, 9.45; $p<0.001$), total carbohydrate (OR: 4.98; 95% CI: 2.69, 9.19; $p<0.001$), GL (OR: 4.25; 95% CI: 2.33, 7.77; $p<0.001$), and GI (OR: 2.51; 95% CI: 1.42, 4.43; $p=0.006$) positively correlated with the risk of T2DM. In contrast, a high dietary fiber intake showed an inverse correlation with T2DM (OR: 0.31; 95 % CI: 0.15, 0.62; $p<0·001$).[122]

Additional analysis of the data from the CURES study population revealed the detrimental dietary habits among South Indian adults (daily energy intake: carbohydrates [64%], fat [24%], protein [12%]) that escalates the risk of T2DM. It was observed that refined cereals contributed to nearly 46% of total energy intake, followed by visible fats and oils (12.4%), pulses and legumes (7.8%), and information of micronutrient-rich foods (fruits, vegetables, fish, etc.) was inadequate and below the recommended standards of FAO/WHO.[124]

Given that carbohydrates are an inherent part of the staple Indian diet and Indians habitually tend to consume high amounts of carbohydrates, improving the quality of carbohydrates in the diet by replacing high-GI carbohydrates with fiber-rich, low GI counterparts.[125] It was observed that consumption of brown rice significantly reduced 24-h glycemic response 24-h ($p=0.02$) and fasting insulin response ($p=0.0001$) in overweight Asian Indians.[126] Replacement of white rice with brown rice was fo be feasible and culturally appropriate in Indian over-weight Indians and correlated with a lower risk of T2DM.[127] Fortification of humble Indian dishes with fiber-rich alternatives, for example, adding soluble fiber in the form of oats in up or improving the glycemic quality of Indian flatbreads (Rotis or chapattis) by adding wheat flour with soluble viscous fibers and legume flour have shown favorable outcomes on the lipid profile and postprandial glucose and insulin responses in T2DM patients.[128–131]

Sugar and sugar-sweetened beverages increase the dietary GL. Overall, the consumption of sugar (25.0 kg/capita) among Indians exceeds the average global annual per capita consumption (23.7 kg). Consumption of sweets, sweetened beverages (e. g., lassi, cameras), and other addition of sugars in curries, gravies, etc. have customary and regional importance in India.[132] In urban South India, the added sugars in hot beverages (tea or coffee) majorly contribute to sugar intake and account for around 3.6% of total GL.[122]

However, fermented foods or beverages produced through controlled microbial growth help to improve the gut microbiome and may improve glycemic control.[133,134]

The low-carbohydrate, ketogenic diet

Low-carbohydrate diets may particularly benefit patients with impaired glucose tolerance and obesity. However, these diets are high in fats and proteins to balance the macronutrient content. Therefore, while adopting such diets, fat intake should occur mainly in the form of MUFA with a parallel decrease in saturated fatty acids (SFAs) and *trans* fatty acids

(TFAs). As the metabolic pathways of carbohydrates and fats are interlinked, low carbohydrate diets high in fats and protein are associated with long-term effects such as ketosis, adverse lipid, and renal outcomes.[135]Evidence suggests that T2DM patients on a low carbohydrate diet achieve favorable outcomes due to reduced energy intake and prolonged calorie restriction, not low carbohydrate intake. Obese T2DM patients should therefore consider switching to a low-carbohydrate diet designed based on calorie restriction and regulated information of fats to reduce the incidence of T2DM and myocardial infarction.[136,137] These diets should be considered for a limited period only. In a small study, overweight patients with T2DM were randomized to a very low carbohydrate ketogenic diet, and lifestyle modifications such as physical activity, sleep, etc. had significantly improved their glycemic control (p=0.002) and lost more weight (p<0.001) than individuals on a conventional, low-fat diabetes diet program.[138]In another similarly designed randomized controlled trial, overweight individuals with T2DM or elevated HbA1c levels on a very low carbohydrate ketogenic diet for 12 months had significant reductions in HbA1c levels (p=0.007) and body weight (p<0.01) than participants on a moderate-carbohydrate, calorie-restricted, low-fat diet.[139]In a 24-week interventional study, a low-carbohydrate ketogenic diet in patients with T2DM favorably improved body weight, glycemic, and lipid profiles in patients with T2DM as compared with patients on a low-calorie diet.[140]

The low glycemic index of pulses and pulse-incorporated cereal foods

Compared with other Western or Asian diets, traditional Indian diets comprising dal, roti, rice, and curry provide a wholesome supply of balanced, mixed nutrients. The mix of various pulses and legumes in a standard Indian meal offers variations in the glycemic and insulinemic indices attributed to the nature of available and non-available (non-starchy polysaccharides) carbohydrates in the foods and alterations in rates of carbohydrate absorption.[141,142] Rice or wheat-based starchy high GI diets reduce the glycemic index and bring satiety and an adequate supply of calories. Meals with mixed sources of Cereals, pulses, and legumes contribute to the regulation of insulin and glycemic responses. Combining acarbose in regular daily diets was associated with a significant decline in postprandial blood glucose in T2DM patients, including those who failed prior treatment with OADs.[143] Similarly, consumption of *adai dosa* (a type of Indian pancake with 75% pulses and 25% cereals) versus a standard diet (75% cereal and 25% pulses) was associated with a reduction in body weight and significant (p<0.01) lowering of HbA1c.[144] Inclusion of nuts (almond, walnuts, cashews, pistachios, hazelnuts) in a diet corresponding to approximately 56 g (1/2 cup) of nuts was associated with a significant reduction in HbA1c (mean difference: − 0.07% [95% CI: −0.10, −0.03%]; p=0.0003) and fasting glucose (mean difference: −0.15 mmol/L [95% CI: −0.27, −0.02 mmol/L]; p=0.03) In individuals with T2DM versus isocaloric diets without nuts. The improvement was mainly attributed to the lowering of GI due to replacement by nuts.[145]In an analysis of dietary patterns in India, diets rich in rice and pulses were associated with a lower risk of diabetes versus diet models with more sweets and snacks.[146] Legumes such as chickpeas are also low glycemic foods and, when substituted for a similar serving of egg, baked potato, bread, or rice, lower the risk of T2DM. They may be beneficial in elderly individuals with CV risk.[147]

Consumption of oils among the Indian population

In the rural South Indian population from the CURES study, the highest intake of fats directly correlated with the risk of abdominal obesity (p<0.001), hypertension (p=0.04), and impaired fasting glucose (p=0.01). In particular, sunflower oil was most detrimental compared to traditional oils and palm olein.[148]A higher percentage of linoleic acid PUFA in sunflower oil was correlated with the risk of metabolic syndrome. Supporting this finding, the risk of metabolic syndrome was higher among users of sunflower oil (30.7%) versus palm olein (23.2%) or traditional (groundnut or sesame) oil (17.1%, p<0.001) in Asian Indians. [52] The observations from these studies are preliminary and should be further investigated. Managing dietary intervention by replacing refined cooking oils with those containing a high percentage of MUFA (canola and olive oil) in Asian Indians with non-alcoholic fatty liver disease was associated with a significant reduction in body weight and BMI (p<0.01, olive oil), improvements in fasting insulin level and insulin resistance and β-cell function by homeostasis model of assessment (p<0.001, olive oil), increase in high-density lipoprotein level (p=0.004, olive oil), and decrease in fasting blood glucose (p=0.03) and triglyceride (p=0.02) level (in canola group).[149]An increase in use of saturated fat, low intake of n-3 PUFAs, and an increase in TFAs were observed among Indian patients with T2DM and obesity, and it is recommended that improve the quality of fats in the diet (more MUFAs and omega-3 PUFAs) would be beneficial in T2DM.[150,151] Reheating/frying or reusing oils at high temperatures, a common practice in India should be avoided as it induces chemical changes that increase the amounts of harmful TFAs, which significantly elevate the risk of CV complications in T2DM patients.[152,153]

Fiber and diabetes mellitus

Increasing the intake of dietary fibers is known to have a favorable effect on overall metabolic health. A high intake of dietary fiber, particularly of the soluble type, above the level recommended by the ADA, improves glycemic control, decreases hyperinsulinemia, and lowers plasma lipid concentrations in patients with type 2 diabetes. Soluble fiber from oats, beans, some nuts and seeds help in regulation of Blood sugar levels, whereas insoluble fiber from whole grains, green leafy vegetables and fruits with edible peels helpsimprove the bowel movement.[154] Fiber-rich foods contain complex carbohydrates resistant to digestion and thereby reduce glucose absorption and insulin secretion.[155–157]In overweight or obese patients with T2DM, a low glycemic index and high-fiber diet significantly (p<0.001) reduce glucose and insulin area under the curve compared with high-glycemic and high carbohydrate diets. The favorable effects on postprandial glucose and insulinemia were sustained for an entire day.[158]Consumption of high-carbohydrate, low-GI diets that contain high proportions of dietary fibers also mitigate the risk of an increase in serum triglyceride levels, a common consequence of a high-carbohydrate diet.[114] Intake of soluble and insoluble fibers has been associated with increased post-meal satiety and decreased consequent hunger episodes.[159] In a randomized, cross-over study in 56 healthy Indian participants, consumption of flatbreads with the addition of fibrous flour such as chickpea (15%) and guar gum (3% or 4%) to wheat flour significantly reduced postprandial glucose (p<0.01) and postprandial insulin (p<0.0001) when compared with flatbreads made from control flour (100% wheat flour).[128]In a dietary assessment study in urban Asian Indians with T2DM, low consumption of dietary fibers (<29 g/day) was associated with a higher prevalence of hypercholesterolemia (p=0.01) and higher LDL (p=0.001) than individuals with a greater median intake of fibers.[160] In a randomized study, daily consumption of 3 g of soluble fiber from 70 g of oats in the form of porridge or up for 28 days in mildly hypercholesterolemic Asian Indians was associated with a significant reduction in serum cholesterol (p<0.02) and LDL (p<0.04) versus the control group (routine diet).[129]From a meta-analysis of 17 prospective cohort studies, an inverse relation was observed between dietary intake and risk of T2DM, based on which it was recommended that intake of 25 g/day total dietary fiber might be optimal for T2DM patients' maintenance.[161]

Physical activity

The International Physical Activity Questionnaire-Long Form and accelerometer can be used to measure and monitor the intensity of physical activity.[162] The intensity of exercise can be measured via the Talk test[163] because of its ease of use with the patients.

- Light intensity: talk and sing comfortably
- Moderate intensity: Talk with some effort, but not sing
- Vigorous intensity: Cannot talk comfortably

Physical inactivity is regarded as a major risk factor for T2DM, and evidence suggests that adequate physical activity may reduce the risk by up to 27%.[125,164] Exercise prescriptions should follow the FITT-VP principle: frequency, intensity, time, type, volume ,and progression.

Along with aerobic exercise resistance training for 2 non-consecutive days a week, exercising all muscle groups is recommended to improve glycemic control, and improve muscle insulin sensitivity. [165]Structured exercises have been found to reduce significantly ($p<0.001$) post-interventional HbA1c levels compared to the control group, which was independent of body weight.[166] In the Indian Diabetes Prevention Program report, lifestyle modification that included a minimum of 30 min/day of physical labor, exercise, or brisk walking showed significant relative risk reductions for T2DM either alone (28.5%; p=0.018) or in combination with metformin (28.2%; p=0.022) versus the control group. [65] In a cross-sectional comparative study, South Asians were found to need an additional 10-15 min/day of moderate-intensity physical activity more than the prescribed 150 min/week to achieve the same cardio-metabolic benefits as the European adults.[167] Resistance training, either alone or in combination with aerobic exercises or walking, has also shown to significantly improve risk factors of T2DM such as waist circumference, abdominal adiposity, HDL levels, etc.[168–170] Based on all available evidence, the ADA and IDF recommend a total of at least 150 min of moderate-intensity physical activity per week, which can be a combination of aerobic activities (such as walking or jogging) or resistance training.[171] For Asian Indians predisposed to develop T2DM or CV risks, an additional 60 min of physical activity each day is recommended, although there is limited data to support this recommendation.[172]

Behavioral lifestyle intervention (BLI) / Behavioral Counseling (BC)

BLI involves patient counseling for strategies such as tailoring goals, self-monitoring, stimulus control, etc., that would help motivate patients to integrate the lifestyle management measures into their day-to-day life and identify and manage potential lapses.[173] BLI approaches have been shown to improve adherence to lifestyle changes and achieve more sustained effects.[174] In patients with T2DM, implementation of a six-month BLI program was reported to significantly reduce HbA1c levels from baseline at three months (–1.56 ± 1.81, $p<0.05$) and six months (−1.17±2.11, $p<0.05$). The BLI used cognitive behavior therapy that mainly involved monitoring carbohydrate intake (using diet charts) and setting targets for weight loss and physical activity across8 sessions (4 face-to-face and four telephone sessions) administered by clinical dietitians.[175] BLI using a smartphone or paper-based self-monitoring of patient behaviors on weight loss and glycemic control (based on Look AHEAD study) in overweight or obese adults with T2DM showed significant improvements in HbA1c (p=0.01) at six months and significant weight loss that was not significant.[176] A systematic review of randomized studies evaluating lifestyle-based interventions for T2DM found that robust behavioral strategies were essential for successfully implementing such prevention programs. This study reviewed the Indian Diabetes Prevention Programme that included individual patient counseling and diet and exercise goal-setting.[177,178] Behavior Counselling approaches are practical in many studies.[179] The regional and cultural differences in the type of diet (especially in India) and subsequently incidence of prediabetes and diabetes are significant, so lifestyle management, especially nutrition, cannot be generalized or one size fits all.Inadequate compliance to lifestyle modifications and medications impacts glycemic control. Compliance with drug is also insufficient (50-60%) [180,181] Diabetes education (HE) has been an integral part of diabetes management. However, most patients may be unable to make a sustainable change by HE alone. BCI or health coaching has been found to have a more significant impact than health education for glycemic control.[182] BCI can be done on constructs of various Behaviour change theories using techniques like the 5 A's or brief Motivational interviewing, which have proved effective. These can be done for individuals or groups. BCI can be facilitated in brief by the clinician who has received short ten-hour training or by a trained professional. While all patients would benefit from BCI, patients with poor glycemic control and complications would benefit more from these interventions and should be given the benefit of this intervention. The barriers to Behaviour counseling interventions (BCI) from a physician's perspective are- Focusing on medically necessary issues, Lack of time, Inadequate clinician training, Low patient demand, and lack of supportive resources.[183]

Sleep, stress and diabetes

Sleep disturbances lead to impairments in metabolism, increases insulin resistance and appetite, and it is recommended that adequate sleep (recommended sleep is 7-8 hours of sleep for adults) contributes to improvement in glycemic control in diabetes. Chronic stress can modulate the glycemic response through various mechanisms including the HPA axis and may have a contributary role as risk, and glycemic control of Diabetes Mellitus Type 2.[184–186]

TREATMENT 1: ORAL HYPOGLYCEMIC AGENTS

Recommendations

Recommended Care

General Principles

- Metformin can be initiated in combination with lifestyle interventions at the time of diagnosis.
- Other options: sulfonylurea (or glinides), TZD, dipeptidyl peptidase-4 (DPP-4) inhibitors, SGLT2 inhibitors, AGIs or oral GLP1-RA can be used initially for cases where metformin is contraindicated or not tolerated.
- Maintain support for lifestyle measures throughout.
- Consider each initiation or dose increase of OADs as a trial, monitoring the response through glucose monitoring (FPG, PPG, self-monitoring of blood glucose [SMBG] or HbA1c) every 2-3 months.
- Consider CV/heart failure risk, renal/hepatic (NASH) risk and other comorbidities while deciding therapy.
- Patient-centric approach: consider cost and benefit risk ratio when choosing OADs.
- Customize therapy focusing on individualized target HbA1c for each patient based on: age, duration of diabetes, comorbidities, cost of therapy, hypoglycemia risk, weight gain, durability.
- Consider initiating combination therapy if the HbA1c >1.5 above the target.
- Metformin should be initiated in combination with lifestyle interventions at the time of diagnosis unless contra-indicated or not tolerated.
- If eGFR is between 45-30 mL/min/1.73m^2: reduce dose of metformin by 50% if already on metformin and avoid starting metformin therapy if not on metformin; stop metformin if eGFR <30 mL/min/1.73m^2. Closely monitor renal function every 3 months.
- In some cases, dual therapy may be indicated initially if it is considered unlikely that single agent therapy will achieve glucose targets or to extend the time to treatment failure.
- Dualtherapy: Patient-centric approach
- If glucose control targets are not achieved: Add (SGLT2) inhibitor, or DPP-4 inhibitor or sulfonylurea or thiazolidinediones (TZDs) or sodium-glucose cotransporter 2 inhibitors, AGI or oral GLP1-RA.
- Individualize patient care based on comorbidities.
- Triple/Quadruple therapy: Patient-centric approach
- If glucose targets are not achieved with two agents: start third oral agent-AGI, DPP-4 inhibitor, SGLT2 inhibitor, or TZDs or oral GLP1RA (depending on the second-line agent used).
- Exceptionally, if target HbA1c is not achieved with 3 oral drugs, addition of a fourth agent with complimentary mode of action to the current OHAs may be considered for glycemic control.
- In the presence of severe IR, addition of TZDs may be considered along with Metformin if not contraindicated.
- For patients with established or having high risk for atherosclerotic cardiovascular disease (ASCVD), heart failure, diabetic kidney disease (DKD) or in need of weight reduction consider using SGLT2 inhibitors or oral GLP1 Agonists.
- For postprandial hyperglycemia, AGI, glinides or SGLT2 inhibitors may be considered if not contraindicated.
- In elderly patients with increased risk of hypoglycemia, use a DPP-4 inhibitor as an alternative to sulfonylurea.

Limited Care

- The principles are same as for recommended care along with considerations for cost and availability of generic therapies. In resource constrained situations, sulfonylurea or metformin or TZDs may be used.
- Newer sulfonylureas have benefit of low cost and reduced hypoglycemia (than older OADs); comparable CV safety with DPP4i may be considered. TZDs have established CV safety and may be considered as add on to metformin.

Background

T2DM occurs due to a complex interaction between genetic inheritance and multiple risk factors such as obesity and sedentary lifestyle etc.[187]Relative Insulin deficiency and/or Insulin resistance, incretin deficiency/resistance, upregulated lipolysis, increased glucose reabsorption from kidney, along with downregulated glucose uptake, neurotransmitter dysfunction, increased hepatic glucose production, and glucagon secretion are the reported metabolic derailments that contribute to hyperglycemia in T2DM [Figure].[188]Among Indians, high familial aggregation, rapid decline in beta cell function, central obesity, insulin resistance, and life style changes due to rapid urbanization are the primary causes of T2DM.[189] Greater degree of insulin resistance paired with higher central adiposity compared to Caucasians is a characteristic feature of T2DM in Asian Indians.[190,191]

Treatment options for T2DM have been developed in parallel to the increased understanding of underlying pathophysiological defects in T2DM. A patient-centric and evidence-based approach that may take into account all the metabolic derailments accompanying T2DM, is now gaining impetus. Therefore, treatments that target factors beyond glycemic control, such as cardiovascular risks, weight management, along with improvements in quality of life have been introduced.[192] Several guidelines/recommendations provide treatment algorithms on ways in which glucose - lowering agents can be used either alone or in combination.

Ideally, treatment decisions should be directed based on glycemic efficacy and safety profiles, along with impact on weight and hypoglycemia risk, comorbidities, route of administration, patient preference, as well as treatment costs.[193]Here the guideline is based on clinical evidences and provides overview on available OADs. The treatment algorithms in this chapter attempt to provide practical recommendations for optimal management of T2DM in Asian Indians.

Considerations

The decision on choice of OAD therapy in T2DM patients is based on the cost, safety, efficacy and comorbidities that were reviewed in Asian Indian context.

Rationale and Evidence

Table 4: Oral antidiabetic agents

	Biguanides	SGLT-2 Inhibitors	Oral GLP-1 Analogues (Semaglutide)	Sulphonylureas	Meglitinides	Thiazolidinediones (Pioglitazone)	DPP-4 Inhibitors	α-glucosidase inhibitors
Expected ↓HbA_{1c}	1.0-2.0	0.8-1.2	1.0-1.5	1.0-2.5	0.5-1.0	0.5-1.0	0.5-0.8	0.5-0.8
Conserve β cell function	No	No	Yes	No	No	Yes	No	No
Hypoglycaemia risk	Very low	Very low	Low	High	Moderate	Very low	Low	Very low
Effects on body weight	NEUTRAL	Weight loss	Weight loss	Weight gain	Weight gain	Weight gain	Neutral	Neutral
Other side effects	GI symptoms	UTI, GENITAL FUNGAL INFECTIONS	Nausea, Higher rates of retinopathy	HYPOGLYCEMIA	HYPOGLYCEMIA	Oedema	None	GI SYMPTOMS
Other safety issues	Lactic acidosis	Increased lower extremity amputation with canagliflozin; ketoacidosis	GI side effects	None	None	Heart failure, fractures	Skin, immune disorders? ARTHRITIS	None
Major cardiovascular event/death	↓CV events	↓CV events	↓CV events	Neutral	Neutral	Neutral CV events	No data (↑ed HF hospitalisation for saxagliptin)	↓CV events
Heart failure risk	↓ed	↓ed	Neutral	Neutral	Neutral	↑ed	↑ed for saxagliptin, alogliptin; neutral for others	Neutral
Renal benefits	None	+++	++	None	None	None	None	None
Benefit on NAFLD	None	++	Not enough data	None	None	+++	None	None
Cost	Low	Upper low	Very high	Low	Low	Low	Low/High	Medium
Overall	++++	+++	+++	++ (depends on salt)	++	++	++	++

Biguanides

Metformin remains the first choice in the management of patients with T2DM where certain new drugs can be used as first line in selected patients.[194]Metformin is efficacious in managing hyperglycemia, increasing insulin sensitivity, along with beneficial effects in reducing cardiovascular and hypoglycemia risk, improving macrovascular outcomes, and lowering mortality rates in T2DM.[195]Metformin is a complex drug that exerts its action via multiple sites and several molecular mechanisms. Metformin is known to down regulate the hepatic glucose production, act on the gut to increase glucose utilization, enhance insulin, increase GLP-1 and alter the microbiome.[196]The UK Prospective Diabetes Study (UKPDS) Group study in over weight T2DM patients suggested that intensive glucose control that(with) metformin lowered the risk of diabetes-related endpoints, diabetes - related deaths, and all-cause

mortality in overweight T2DM patients, compared to insulin and sulphonylureas.[197] A 10-year follow-up study of the UKPDS reported continued benefit following intensive glucose control with metformin in terms of reduced diabetes-related endpoints, diabetes - related deaths, and all-cause mortality.[198] Along with substantial improvements in hyperglycemia, metformin improved endothelial dysfunction, oxidative stress, insulin resistance, lipid profiles, and fat redistribution.[199] Owing to the concerns of lactic acidosis and gastrointestinal effects (nausea, vomiting, diarrhoea and flatulence) metformin should be used cautiously in patients with renal insufficiency or elderly patients. In patients with an eGFR <60 mL/ min/1.73 m^2 metformin can be used, but should not be initiated in patients with an eGFR of 30 to 45 mL/min/1.73m2 and must be contraindicated in patients with an eGFR below 30ml/min/1.73m2. Long term Use(>5yrs) of Metformin is associated with vitamin B12 deficiency and worsening of neuropathy. So, the periodic measurement of vitamin B12 level is suggested.

Sulfonylureas

Sulfonylureas can be used as second line agents in patients with T2DM patients who are not obese. Sulfonylureas are insulin secretagogues that act on the ATP-sensitive K+ channels on the β cells and stimulate endogenous insulin secretion.[200] As a single therapy, sulfonylureas are efficacious in lowering fasting plasma glucose and HbA1c. However, concerns of modest weight gain and moderate to severe hypoglycemia and cardiovascular risk limit their clinical benefits.[201]As a consequence of closure of cardiac K channel, the use of sulfonylureas (Eg: Glibenclamide) have also been related to adverse CV effects due to impaired hypoxic coronary vasodilation during increased oxygen demands such as acute myocardial ischemia.[202]The use of glibenclamide was associated with an increased risk of in-hospital mortality in patients with diabetes and acute myocardial infarction.[203] Adverse cardiovascular outcomes with sulfonylureas in some observational studies have raised concerns, although findings from recent meta-analysis that included several RCTs reported that sulfonylureas when added to metformin were not associated with all- cause mortality and CV mortality.[204] New generation sulfonylureas have demonstrated superior safety, mainly due to reducing hypoglycemia, and improved cardiac profile. Sulfonylureas particularly gliclazide modified release (MR) and glimepiride have a lower risk of hypoglycemia and are preferred in south Asian T2DM patients.[205] Caution must be exercised while prescribing sulfonylureas for patients at a high risk of hypoglycemia, older patients and patients with CKD.[206] Shorter-acting secretagogues, the meglitinides (or glinides), also stimulate insulin release through similar mechanisms and may be associated with comparatively less hypoglycemia but they require more frequent dosing. Moreover, modern sulfonylureas exhibit more reductions of HbA1c than glinides.[207]

Thiazolidinediones

Drugs from this class are peroxisome proliferator activated receptor γ activators that improve insulin sensitivity by increasing insulin-mediated glucose uptake in skeletal muscle, suppressing hepatic glucose output, and improving the secretory response of insulin in pancreatic β-cells.[208] The risk of hypoglycemia is negligible and TZDs may be more durable in their effectiveness than sulfonylureas.[209] TZDs have been constantly under the authority scrutiny for their cardiovascular safety. A meta-analysis considering data from 42 trials and 27,847 patients indicated that treatment with rosiglitazone was associated with an increase in the odds of MI (odds ratio 1.43, 95% CI 1.03 to 1.98, p=0.03) and a nonsignificant increase in the odds of cardiovascular death (odds ratio 1.64, 95% CI 0.98: 2.74, p=0.06) compared with a control group (active comparator or placebo).[210]Pioglitazone is known to exert pleotropic effects on cardiovascular event; pioglitazone improves endothelial dysfunction, lowers hypertension, improves dyslipidemia, and lowers circulating levels of inflammatory cytokines and prothrombotic factors.[211] In the PROactive study, pioglitazone lowered the composite of all-cause mortality, non-fatal myocardial infarction, and stroke in T2DM patients with at risk of macrovascular events along with improvements in HbA1c, triglycerides, LDL, and HDL levels. However, rate of heart failure was increased.[212]TZDs have demonstrated beneficial effects in attenuating dyslipidemia commonly observed in patients with chronic T2DM. Furthermore, the IRIS trial was among the 1st studies to document the CV benefits of TZDs in non-diabetic individuals. Pioglitazone improved CV outcomes (recurrent stroke and MI) and prevented the development of T2DM in insulin-resistant, non-diabetic patients with cerebrovascular disease.[213] In a recent post hoc study of the IRIS trial, conducted in prediabetic population, pioglitazone effectively lowered the risk of stroke, MI, acute coronary syndrome, and hospitalization for heart failure.[214]Pioglitazone has been found to have an additional benefit of significantly alleviating NASH in patients with prediabetes or Type 2 Diabetes Mellitus combined with NAFLD. Pioglitazone had been linked with a possible increased risk of bladder cancer, possibly in a dose-and time-dependent manner.[215] However data from a retrospective study in India involving 2222 (pioglitazone users, n = 1111; pioglitazone non-users, n= 1111) T2DM patients found no evidence of bladder cancer in any of the groups, including patients with age >60 years, duration of diabetes >10 years, and uncontrolled diabetes.[216] Recognized side effects of TZDs include weight gain (3–5 kg), fluid retention leading to oedema, and/or heart failure in predisposed individuals and patients with increased risk of bone fractures.[209,212,216]

Dipeptidyl peptidase-IV inhibitors

Vildagliptin, saxagliptin, alogliptin, evogliptin sitagliptin, teneligliptin, and linagliptin are incretin enhancers; they enhance circulating concentrations of active GLP-1 and gastric intestinal polypeptide (GIP).[217] These incretins stimulate insulin secretion, suppress glucagon synthesis, lower hepatic gluconeogenesis, and slow gastric emptying. Their major effect is the regulation of insulin and glucagon secretion; they are weight neutral.[218] DPP-4 inhibitors are efficient in improving glycaemia both as monotherapy and as add-on to metformin, sulfonylurea and TZDs in patients with inadequate glycemic control. A reduction in HbA1c levels from baseline of 8.1% was observed with sitagliptin monotherapy (100 mg: -0.5%, 200 mg:- 0.6%) in 521 patients treated for 18 weeks. Additionally, homeostasis model assessment of beta cell function index, fasting proinsulin-insulin ratio which are the markers of insulin secretion, and beta cell function were also improved significantly.[219] The overall incidence of adverse events with sitagliptin is comparable to other OADs when used as monotherapy or as add-on to existing OADs.[220] Adverse effects (AEs) such as constipation, nasopharyngitis, urinary tract infection, myalgia, arthralgia, headache, and dizziness are the commonly reported AEs with the use of these agents.[221] Cardiovascular outcomes trial (CVOT) studies with DPP-4 inhibitors have shown that these agents are safe in patients with established CVD and those at increased risk of CVD except for increased risk of heart failure risk.[222]TECOS Trial had proven CV safety for sitagliptin and no additional excess hospitalization for heart failure.[223]Results of the SAVOR-TIMI study and EXAMINE Study have reported higher rates of hospitalization for heart failure with saxagliptin and alogliptin, respectively.[224,225]Owing to the increased risk of hospitalization due to heart failure in patients with cardiovascular disease, the US FDA issued a warning, suggesting the associated risk to be a "class-effect" of the DPP-4 inhibitors and issued a warning for their use.[226] However, some landmark studies have been conducted to evaluate relationship between these drugs and the adverse effects. In the CARMELINA study, linagliptin demonstrated a long-term CV safety profile in patients with T2D, including those with CV and/or kidney disease and no increased risk of hospitalization for heart failure versus placebo was reported.[227]The CAROLINA study was designed to evaluate the long-term CV safety profile of linagliptin versus glimepiride in patients with early T2D at increased CV risk. The study results highlight a non-inferiority between linagliptin versus glimepiride in time to first occurrence of CV death, non-fatal MI, or non-fatal stroke (3P-MACE) with a median follow-up of more than 6 years.[228]

Sodium-glucose co-transporter 2 inhibitors

They provide insulin-independent glucose-lowering by blocking glucose reabsorption in the proximal renal tubule. The capacity of tubular cells to reabsorb glucose is reduced by SGLT2 inhibitors leading to increased urinary glucose excretion and consequently, correction of the hyperglycaemia.[229] Dapagliflozin, canagliflozin, empagliflozin, and remogliflozin are the 4 Drug Controller General of India (DCGI) approved agents used in patients with T2DM.[230,231]In The EMPA-REG OUTCOME trial, patients with Type2 diabetes with high risk of cardiovascular events and estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73 m2, who received empagliflozin, as compared with placebo, had significantly lower rate of the primary composite cardiovascular outcomes and all-cause mortality. Empagliflozin reduced the rate of new onset or worsening nephropathy, which were defined as new-onset microalbuminuria, doubling of creatinine, and eGFR ≤45 mL/min/1.73 m^2, initiation of renal replacement therapy, and death due to renal disease (hazard ratio [HR]: 0.61, 95% CI: 0.53, 0.70; p<0.0001).[232]The CANVAS Program integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk. Treatment with canagliflozin showed a possible benefit with respect to the progression of albuminuria (HR: 0.73; 95% CI: 0.67, 0.79) and the composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal- replacement therapy, or death from renal causes (HR: 0.60; 95% CI: 0.47, 0.77).[233]Canagliflozin in combination with metformin significantly improved glycemic control in patients with T2DM and significant weight loss along with low incidence of hypoglycemia have been reported.[234] A recent meta-analysis concluded that SGLT2 inhibitors, as a class, significantly reduce 24-h ambulatory blood pressure further substantiating their favorable cardiovascular profile.[235] The most common AEs involving this class are genital mycotic infections, which are believed to be mild and respond favorably to antifungal therapy.[236–240]

In CREDENCE trial, in the patients with Type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in the Canagliflozin group compared to the placebo group.[241]

In DAPA HF Trial, the patients with heart failure with reduced ejection fraction, those who received Dapagliflozin had a lower risk of worsening heart failure and cardiovascular death.[242]

Alpha glucosidase inhibitors

These agents delay the absorption of consumed carbohydrates by competitively inhibiting the α-glucosidase enzymes at the enterocyte brush border. This inhibition delays the digestion of starch and sucrose and maintains levels of postprandial blood glucose excursions.[243] The action of these agents is independent of insulin action and hence are devoid of hypoglycemic adverse effects. In the Essen-II Study, conducted in 96 patients, acarbose significantly lowered HbA1c levels when compared with placebo and treatment with acarbose was associated with a weight reduction of -0.8 kg.[244] When added to background of metformin, treatment with acarbose led to HbA1c reduction of 0.7%.[245]The AGIs have demonstrated an acceptable safety profile with major complaints being of flatulence and diarrhea.

The glucose-lowering effectiveness of OADs is said to be high with metformin, sulfonylureas, and TZDs (expected HbA1c reduction ~ 1.0–1.5%) and comparatively lower for meglitinides, DPP4 inhibitor, SGLT2 inhibitor, AGIs.[221]

However, older drugs have typically been tested in clinical trial participants with higher baseline HbA1c, which is associated with greater treatment emergent glycemic reductions, irrespective of therapy type. In head-to-head trials, any differential effects on glucose control between different OADs are small. So, agent and patient-specific properties, such as ease of administration, dosing frequency, side effect profiles, cost, and other benefits, often help in their selection.

Oral Glucagon Like Peptide1 Receptor Agonist

Oral semaglutide is world's first oral GLP-1RA approved for the management of Type 2 diabetes in adult population. Oral Semaglutide is the latest addition to the oral antidiabetic agents. The development of this drug is the result of significant innovation in the oral drug delivery with the use of absorption enhancer. It has significant HbA1c lowering efficacy along with significant weight reduction. It is safe for mild to moderate renal impairment. This drug will play an important role in the management of Type2 diabetes with obesity for those preferring oral therapy.

Oral semaglutide has undergone a clinical trial program named as PIONEER trials. Oral semaglutide showed significant HbA1c and weight reduction in comparison to sitagliptin, empagliflozin and injectable liraglutide. Oral semaglutide has shown HbA1c reduction up to 1.5 % and weight reduction up to 5 kg at end of 26 weeks. Approximate 50 % of patients achieved >5 % of weight loss. Oral semaglutide has shown to be CV safe in PIONEER 6 trial and shown 21% non-significant reduction in MACE. Oral semaglutide has also shown reduction in CV risk factors like dyslipidemia, systolic blood pressure and hsCRP levels [246–249]

Oral semaglutide has safety profile similar to other injectable GLP-1Ras. The most common side effects are gastrointestinal events (nausea, vomiting and diarrhea). These are usually mild to moderate in nature and go away with time.

Oral semaglutide can be used in addition to metformin or as a monotherapy if metformin is contraindicated. Oral semaglutide can be used across e GFR without any dose adjustment. [246–250]The main disadvantage of this is the cost of the drug.

Miscellaneous Anti-Diabetic Drugs

- Hydroxychloroquine HCQ has been approved by DCGI for selected patients in which blood sugar levels are not controlled with two antidiabetics.
- Saroglitazar can be used in diabetic patients with hypertriglyceridemia and NASH with the additional advantage of mild HbA1c reduction.
- Bromocriptine
- Colesevelam

These drugs have been used as adjuncts with other antidiabetics.

However, older drugs have typically been tested in clinical trial participants with higher baseline HbA1c, which is associated with greater treatment-emergent glycemic reductions, irrespective of therapy type. In head-to-head trials, any differential effects on glucose control between different OADs are small. So agent and patient-specific properties, such as ease of administration, dosing frequency, side effect profiles, cost, and other benefits, often help in their selection.

- Two-drug combination therapies with metformin (such as metformin plus TZDs, metformin plus sulfonylureas, metformin plus SGLT2 inhibitors, and metformin plus DPP4 inhibitors, DPP4+ SGLT2) were more effective in reducing HbA1c than metformin monotherapy by about 1%.[251] In addition, triple FDC of metformin and sulfonylurea plus pioglitazone are also available in India.
- RSSDI wheel given along with this recommendation book will help practitioners choose an ideal drug for his patient based on cost, weight, hypoglycemia risk, and other comorbid conditions.

TREATMENT 2: INJECTABLES

Recommended Care

- » Insulin therapy should be considered in all patients failing to achieve glycemic targets on three oral agents. However, additional oral agents can be considered in subjects with HbA1c 1% to 1.5% above the mark. Clinicians must consider the limitations of individual oral agents or their combinations in terms of the quantum of HbA1c reduction.
- Consider initiating Insulin in type-2 diabetes patients with severe symptomatic hyperglycemia or unstable state.
- A three-step protocol involving initiation, titration, and intensification is recommended for all patients requiring insulin.
- **Initiation**
  - "Providers should avoid using insulin as a threat or describing it as a sign of personal failure or punishment and should work to alleviate patient's anxiety about hypoglycemia, dependence, injection-site pain, etc., commonly attributed to insulin."
  - Therapeutic choice of regimen, preparation, and the delivery device should be made through shared, informed decision making.
  - Initiate with once-daily basal insulin, once-daily premixed/co-formulation insulin, or twice-daily premixed insulin, either alone or in combination with other OADs, based upon patient's age, clinical features, glucose profile, risk of hypoglycemia, and patient preference. Basal insulin may also be initiated in combination with GLP-1 analogs.
  - Basal bolus insulin regimens may be needed in severe hyperglycemia, and life-threatening or organ/limb threatening clinical situations.
  - Analogue insulins may be used in preference to human insulins with a possible lower risk of nocturnal and symptomatic hypoglycemia; however, economic considerations must be taken into account.
  - Meal timing should match with insulin dose.
  - Counselling/education about SMBG, hypoglycemia prevention/recognition, and treatment are recommended for all patients initiating insulin.
  - Guidance adjusting insulin dose adjustments, administration, storage, and other practical aspects should be made available.
- **Titration**
  - Initiate insulin as defined in the algorithm, using a self-titration regimen (dose increases of 2–4 Units (U) weekly or biweekly) or with more frequent contact with a healthcare professional.
  - Aim for pre-meal glucose levels of <115 mg/dL and PPG levels of <160 mg/dL. These targets can be individualized based on the risk of hypoglycemia and the urgency for glycemic control. Subjects with an increased risk of hypoglycemia <130 mg/dl and <180 mg/dl should be optimum.
  - Titration should be done to control FBG first, followed by prandial control. However, if premixed or co-formulation is used, then FBG and pre-dinner glucose can be targeted simultaneously. Meal with highest glycemic excursion in sequential order.
- **Intensification**
  - Intensification of insulin therapy is recommended when patients fail to achieve glycemic goals even after optimal dose titration.
  - Several options can be considered during intensification. In patients on basal insulin-
    - » Switch to premix insulin twice-daily or premix analogs twice or thrice-daily
    - » Switch to insulin co-formulation-based regimen
    - » Add prandial insulin (basal plus or basal-bolus) with the largest meal of the day
    - » Add GLP-1 analogs
  - The choice of intensification strategy should be based upon dietary pattern, lifestyle, risk of hypoglycemia and weight gain, affordability, and patient preference.
  - Basal plus regimen can be used as a stepwise approach to insulin intensification, leading to basal-bolus prescription. It is associated with a lesser risk of hypoglycemia and weight gain than the basal-bolus regimen.
  - Both premix insulin therapy and co-formulation insulins are acceptable methods of intensification. Co-formulation insulin offers the advantage of lower risk of hypoglycemia and nocturnal hypoglycemia. This also has the advantage of lesser nocturnal hypoglycemia and lesser insulin dosage than the Basal plus or basal-bolus regimen.
  - Follow insulin intensification as recommended in the algorithm.
- **GLP-1 analogs**
  - GLP-1 analogs with proven CV benefits should be considered to reduce the risk.
  - Viable second-line or third-line options for managing patients with uncontrolled hyperglycemia.
  - Can be considered in overweight/obese patients as second-line therapy in patients with metformin inadequacy and first-line therapy in patients with metformin intolerance.

To be added to insulin therapy, preferably basal insulin only if glycemia goals are not achieved with reasonably high dose insulin doses if unacceptable weight gain or hypoglycemia occurs. Dose reduction of insulin may be needed in such cases. Transient gastrointestinal side effects may occur.

Limited Care

- All conventional insulins have similar glycemic lowering efficacy as analogs but with a slightly increased risk of hypoglycemia and lack of administration flexibility.
- Insulin supplies should be assured and be of consistent quality and type.

Background

Most treatments available to control glycemia impact the pathways targeting β-cells or insulin resistance (IR). Their efficacy depends upon the presence of insulin for their therapeutic effect. The durability of these medications varies, and their safety is occasionally under scrutiny. Over a period, patients fail to achieve or maintain HbA1c levels even with multiple OADs and will require insulin therapy. Although insulin is the most effective option for glycemic control, it should not be used as a first-line treatment in T2DM, as it can predispose to hypoglycemia, weight gain, and large doses over prolonged duration might increase the risk of malignancy and cardiovascular diseases. However, it is equally essential to ensure timely initiation of insulin without delay once optimal combinations of oral hypoglycemic drugs have failed to achieve the target HbA1c.

Most guidelines recommend early short-term insulin therapy in patients with high HbA1c at the time of presentation in subjects with catabolic symptoms.[252–254] Landmark trials in the last decade suggest that glycemic control should be intensive in the early stages of diabetes, preferably in the first four years of diagnosis, to create an excellent metabolic memory.[197,255,256] The traditional postponement of insulin therapy up to the prolonged failure of lifestyle and oral agents to achieve glycemic control has been revised in the last decade to incorporate insulin therapy much earlier, often in combination with OADs or GLP-1 analogs to reduce long term micro vascular and macro vascular complications. Non-insulin injectables such as GLP-1 and amylin analogs (pramlintide) have been approved in various countries. The GLP-1 analogs improve glycemic control through multiple mechanisms, have a low risk of hypoglycemia, and provide clinically relevant weight loss.[257] As pramlintide is unavailable in India, these recommendations will not cover it.

Consideration

The decision on injectable therapy in T2DM patients is based on clinical, pharmacological, and psychosocial factors. Additionally, local factors such as cost, quality, cold chain maintenance, and perennial availability of insulin preparations and delivery devices must be considered in the Indian context.

As suggested above, if optimal doses of three or more (in selected subjects) oral antidiabetic agents for 3–6 months fail to achieve HbA1c targets or organ dysfunction contraindicates the use of oral agents, the addition of insulin may be justified. The landmark studies support this idea and suggest that gaining intensive Glycemic control (if not contraindicated) is profoundly beneficial in the initial few years of diagnosis.

Insulin may be started with two oral drugs, which have the advantage of weight reduction, no hypoglycemia, and cardio-renal benefits. However, in the majority, Insulin should be used with metformin if the latter is not contraindicated and is well tolerated. As the patient's glucose toxicity resolves, the regimen can potentially be de-escalated, and a switch over to oral therapy may be considered.

HbA1c targets must be determined as criteria set for individualized therapy efficacy of each agent as combination therapy must be considered.[258]The near-normal glycemic target of 6.5% should be considered for younger patients with recent onset of T2DM with few or no micro or macrovascular complications. In comparison, slightly higher HbA1c targets may be considered for older patients with long-standing T2DM and evidence of CVD, organ failure, and terminal illnesses.[259]

While initiating insulin, doses of OADs should be modified as follows:

- No change in metformin doses, DPP4i, SGLT 2 inhibitors, AGI and TZDs.
- Dose of sulphonylureas should be reduced when prandial insulin is introduced.
- Risk of unacceptable weight gain should be kept in mind while prescribing insulin with TZDs and the latter should be withdrawn if such weight gain is seen.

(Adequate doses of oral agents do not necessarily mean the highest administrable doses because, in most cases, doubling the doses of these medicines does not necessarily increment their effects.)

Rationale and Evidence

The insulin strategy

While initiating the insulin therapy, the following features have to be considered; choosing the appropriate regimen, identifying the proper preparation, prescribing the available strength of the molecule, matching it with the correct delivery device, deciding the proper insulin dose, and following the optimal titration strategy.

Ideally, an insulin treatment program should be designed specifically for the individual patient, matching the insulin supply to his/her dietary/exercise habits and prevailing glucose trends as revealed through self-monitoring. Anticipated glucose-lowering effects should be balanced with the convenience of the regimen in the context of an individual's specific therapy goals.

Patient Education

Proper patient education regarding monitoring of glucose, insulin injection technique, insulin storage, recognition/treatment of hypoglycemia and sick day management is imperative. Diabetes educators, where available, are invaluable in guiding patients through their treatment.

Table 5: Clinical situations where the use of injectables is recommended

Short term insulin	GLP-1analogss	Basal insulin + GLP-1
Catabolic symptoms High glycemic parameters: HbA1c >9.0%, FPG >200 and/or PPG >300 mg/dL Acute diabetic complications/medical conditions Hospitalized patients not suitable for OADs: Perioperative, transplants, critical care units Pregnancy	Recommended as the first injectable option in subjects failing on optimum combination of oral drugs (standard care): Concomitant CVD, CKD, Where hypoglycemia and weight gain must be avoided	Recommended in cases where further intensification of therapy is required

CKD: Chronic kidney disease, CV: Cardiovascular, CVD: CV disease, HbA1c: Glycosylated hemoglobin, OADs: oral antidiabetics, FPG: Fasting plasma glucose, GLP-1: Glucagon-like peptide 1, PPG: Postprandial glucose

Adverse events and barriers

Hypoglycemia is a significant safety concern with insulin treatment and can be a barrier to initiation or intensification.[260]Addition of Sulphonylurea and TZDs can accentuate the risk of weight gain with insulin treatment [261]. However, addition of SGLT 2 inhibitors and Oral or injectable GLP-1 RA are likely to mitigate the weight gain caused by Insulin. Combination with DPP4 inhibitors results in weight neutrality, and combination with metformin or AGIs in combination may produce weight loss compared with insulin monotherapy.[262]

Insulin use is hindered by a variety of social barriers. A recent National Insulin Summit (NIS) consensus lists the barriers to insulin therapy related to patient/community, physician/provider, and drug/device and proposes different bridges to overcome these hurdles. Patient-related barriers such as the inability to inject, monitor, or titrate the insulin dose, weight gain, hypoglycemia, and lack of awareness of uncontrolled diabetes can be bridged with patient education and training, support and counselling and social marketing. Physician and provider barriers such as inadequate communication or motivation skills, inability to initiate, optimize or intensify insulin, and lack of awareness may be addressed through relevant skill development training and continuing medical education (CME). Furthermore, drug or device-specific barriers such as suboptimal effects of insulin, lack of flexibility, and device discomfort can be surmounted through CME, flexible insulin regimens and preparations and modern devices.[263]

Initiation of insulin therapy

Premixed/co-formulation or basal insulin are usually initiated as initial therapy unless the patient is experiencing a medical, surgical, or obstetric crisis or metabolic decompensation.[194,252,254,264] General concept is to first correct the fasting hyperglycemia with a dinner/bedtime injection and then address postprandial hyperglycemia. However, IDeg Asp (co-formulation) is to be used preferably before the largest meal of the day.

Choice of initial insulin is often dictated by subjective features such as disease severity and the patient's ability to self-inject at specific times of the day [Table 4]. Even though FPG and PPG measurements provide sufficient information to choose an insulin type, it is difficult to make an appropriate decision when they are considered separately. Similarly, the choice of insulin based on the HbA1c value alone can be challenging.[265] All international and Indian guidelines recommend insulin initiation with basal or premixed/co-formulation insulins except ADA/EASD and AACE guidelines which prefer basal insulin for initiation.

Intensification of Insulin therapy (Tables # and ##)

Most patients with T2DM requiring insulin therapy can be successfully treated with one or two doses; a few may require a third dose of premix insulin or a basal plus followed by bolus therapy requiring three to four doses.

Table 6: Choice of insulin therapy

Basal insulin	Premixed/co-formulation OD or BID	Prandial insulin
HumanNPH; glargine U100; glargine U300; detemir; degludec	**Human premixed (30/70 or 50/50); BiAsp 30/70; LisproMix 25/75; IDegAsp 30/70**	**Human regular; Lispro Aspart; glulisine; FiASP** **Inhaled insulin**
All have equal efficacy Duration of action: Degludec > glargine U300 > glargine U100 > detemir > NPH NPH, detemir, and glargine U100 may need to be given twice daily High doses of glargine U100 beyond 0.5 U/kg body weight should be split to avoid hypoglycemia Starting dose: 10 U of basal insulin followed by weekly or biweekly titration Degludec and glargine U300 cause the least hypoglycemia with no tailing effect of hyperglycemia Glargine U300 requires 20% extra doses, but a lesser volume is required Glargine U300 can be used where a high volume of insulin is required Detemir causes the least weight gain Basal insulin should be given preferably at bedtime to achieve adequate suppression of HGP NPH and detemir are approved for use in pregnancy and with steroid use	All have equal efficacy Most patients should be initiated with either a co-formulation or premixed 30/70 or 25/75. In subjects with uncontrolled PPG-premixed 50/50 can be used before the meal showing highest excursion Starting dose: 10 U OD or 6 U BID followed by weekly or biweekly titration IDegAsp does not produce shoulder effect 4-6 h post-injection as observed with BiAsp 30/70 or LisproMix 25/75 IDegAsp causes the least hypoglycaemia requires fewer dose, and causes the least weight gain IDegAsp has the flexibility of administration before any large meal of the day and can be given with different meals on different days BiAsp 30/70 and LisproMix 25/75 are approved for use in pregnancy	To be administered when an individual fails to achieve glycemic targets following basal insulin HbA1c above target with ~0.5 U/kg/day of daily basal insulin Elevated HbA1c despite normal FPG (in the absence of available PPG readings) with basal insulin FPG with basal insulin is within the targeted range, but PPG is persistently above the goal. Further increase in basal insulin results in hypoglycemia

BID: Twice daily, BiAsp: Biphasic insulin aspart, IDegAsp: Mix of insulin degludec and insulin aspart, NPH: Neutral protamine Hagedorn, OD: Once daily, HGP: Hepatic glucose production, FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin, PPG: Postprandial glucose

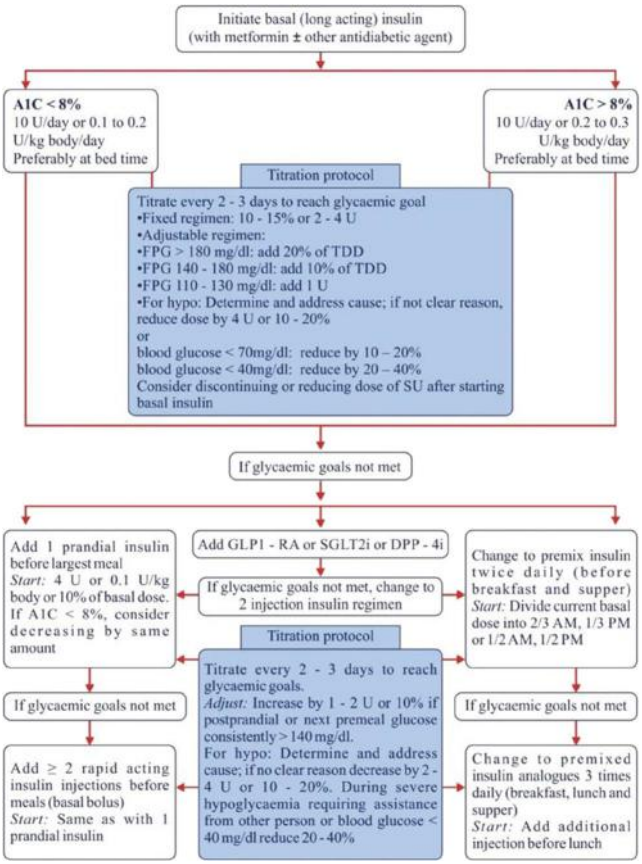


Figure 2: Approaches for initiating insulin. [266] OD: Once daily; BID: Twice daily; TID: Three times a day; GLP-1 RA: Glucagon-like peptide-1 receptor agonist; IAsp: Insulin Aspart; IDegAsp: Mix of insulin degludec and insulin aspart; A1c: Glycated hemoglobin; DPP-4i: Dipeptidyl peptidase-4 inhibitors; FPG: Fasting plasma glucose; GLP-1 RA: Glucagon-like peptide-1 receptor agonist; SGLT2i: Sodium-glucose co-transporter 2 inhibitors; TDD: Total daily dose

Basal plus regimen requires regular insulin administered about 30 min before meals or rapid insulin analogs such as insulin lispro (ILis), insulin aspart (IAsp), or insulin glulisine (IGlu), which can be injected just before or with the meal. They result in better PPG control than human regular insulin.

Glucagon-like peptide-1 analogs:

The injectable GLP-1 analogs like liraglutide, exenatide, lixisenatide, dulaglutide, and albiglutide imitate the effects of Endogenous GLP-1, stimulate pancreatic insulin secretion in a glucose-dependent fashion, suppress pancreatic glucagon output, slow gastric emptying, and decrease appetite. Their main advantage is weight loss, which can be significant in some patients. The limiting side effects of these agents are nausea and vomiting, particularly early in the course of treatment.[267] In combination with basal insulin, they have proved to be extremely useful for intensification because of additive action (IDegLira, Lixilan). Individual agents in this class should be initiated and optimized as per recommended schedules.

There have been concerns regarding an increased risk of pancreatitis with GLP-1 analogs but recently published

Table 7: Steps for initiating basal insulin

Step 1:	Glucose Value HbA1c <8%	TDD 0.1-0.2 U/kg
Step 2: Titration# (every 2-3 day to reach FPG target)	HbA1c >8% Fixed regimen Adjustable regimen FPG >180 mg/dL FPG 140-180 mg/dL FPG 110-139 mg/dL	0.2-0.3 U/kg Increase by 2 U/day Add 4 U Add 2 U Add 1 U
Step 3: Monitor for hypoglycemia	BG <70 mg/dL BG <40 mg/dL	Reduce by 10%-20% Reduce by 20%-40%

*Consider decreasing the dose of the SU therapy, and basal analogs should be preferred over NPH insulin, #For most patients with T2DM taking insulin, glucose goals are HbA1c <7% and fasting and premeal BG <115 mg/dL in the absence of hypoglycemia. HbA1c and FPG targets may be adjusted based on the patient's age, duration of diabetes, comorbidities, diabetic complications, and hypoglycemia risk. DM: Diabetes mellitus, BG: Blood glucose, FPG: Fasting plasma glucose, HbA1c: Glycosylated hemoglobin, NPH: Neutral protamine Hagedorn, SU: Sulfonylureas, T2DM: Type 2 DM, TDD:

Table 8: Titration algorithm

Basal insulin	Prandial insulin	Premixed insulin
Given preferably at bedtime to achieve adequate hepatic glucose production (HGP) suppression, Target: FPGL <115 mg/dl Initiate with 10 U at bedtime and check FBS Increase dose by 2U weekly or biweekly by patient self-titration till target FBSL is achieved. BID: Two times daily, BG: Blood glucose, FBG: Fasting BG, FBSL: Fasting blood sugar level, FPG: Fasting plasma glucose, HGP: Hepatic glucose production, PPG: Postprandial glucose	Initiate along with meal with highest glycemic excursion Start with 4 U and increase by 1 U/day or 3 U/3 days till PPG <180 The next meal with the highest glycemic excursion should be titrated similarly Full basal-bolus can be considered for effective prandial control after all meals	Calculate the total dose Start with 6 U BID day for analogs and 2/3 dose in the morning and 1/3 dose in the evening for human insulins Titration can be done for morning dose based on predinner values and for evening dose based on FBG 1 U/day or 3 U/day to achieve the required BG targets

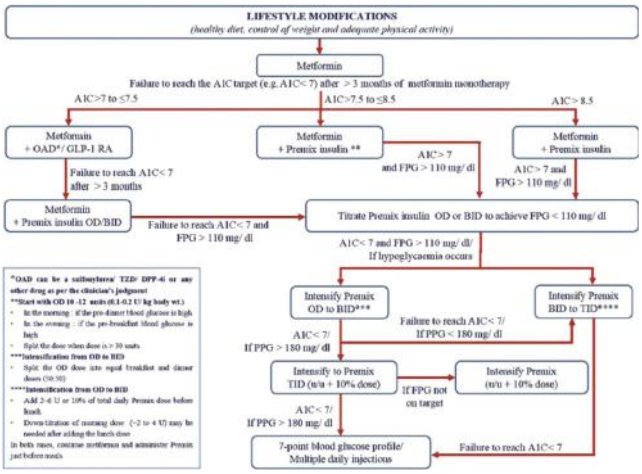


Figure 3: Steps for initiating premixed insulin. OAD: Oral antidiabetic agents; GLP-1 RA: Glucagon-like peptide-1 receptor agonist; OD: Once-daily; BID: Twice-daily; TID: Thrice-daily; TZD: Thiazolidinedione; DPP-4I: Dipeptidyl peptidase-4 inhibitors

ELIXA and LEADER studies do not show any increased risk of pancreatitis, pancreatic cancer, or thyroid cancer with lixisenatide or liraglutide.[268,269]

Furthermore, in the LEADER trial, the primary composite outcome of the first occurrence of death from CV causes, non-fatal MI, or non-fatal stroke was significantly less with liraglutide as compared to placebo (HR, 0.87; 95% CI: 0.78, 0.97; p<0.001 for non-inferiority; p=0.01 for superiority).[269] Based on this result, liraglutide is approved for its CV benefits as well by FDA "as an adjunct to standard treatment of CV risk factors to reduce the risk of major adverse CV events (CV death, non-fatal MI, or non-fatal stroke) in adults with T2DM and high CV risk.[270]

Implementations

A challenging aspect of diabetes care is the timely initiation and intensification of injectable therapy. This must be addressed by focusing on patient education and motivation and updating health care professionals' knowledge. Lifestyle modification, self-monitoring, and insulin education should be integral parts of insulin therapy in T2DM. Structured guidelines and protocols should be shared, and glycemic audits of persons on oral medications should be performed to address the issue.

Table 9: Insulin intensification options

Insulin regimen	Characteristics
Basal plus regimen	One basal insulin along with one prandial insulin before the meal shows the most considerable PPG excursion Advantages: Flexibility and can be further intensified to cover 2 or 3 meals (complete basal-bolus regimen) Disadvantages: Needs two insulins, two pens, and two different titrations for individual components bringing in complexity in the regimen
Premixed insulins BID or TID	If used thrice daily, then the afternoon dose should be 4-6 U to start with, and the morning dose to be reduced by 10%-20%
Co-formulation IDegAsp	BID is sufficient and is as effective as the basal-bolus regimen Can be given before any two large meals of the day so long as the interval between two injections is six h (corresponding to the time action profile of the aspart component) Compared with the Basal plus regimen twice-daily, IDegAsp causes similar efficacy, lesser nocturnal hypoglycemia, and has the convenience of one insulin and one pen Compared with the basal-bolus regimen, IDegAsp causes identical reductions in HbA1c, lesser hypoglycemia, requires lesser doses, more secondary weight gain, and is simple to administer
Basal bolus regimen	Most physiological and most effective regimen for intensification Requires one or two injections of basal insulin, and three injections of prandial insulins Complex regimen and requires an understanding of different titration schedules for basal and prandial components. Knowledge of carbohydrates counting is desirable for proper dosing of prandial component It needs persistent monitoring, which could be painful and expensive

BID: Twice daily, IDegAsp: Mix of insulin degludec and insulin as part, PPG: Postprandial glucose, TID: Thrice daily, HbA1c: Glycosylated hemoglobin

Table 10: Steps for intensification of insulin therapy

	Therapeutic option	TDD
Step 1: Add prandial insulin	When glycaemic targets are unmet	TDD 0.3-0.5 U/kg (40%-50% basal: 50%-60% prandial) *
Step 2: Titration# (every 2-3 days to reach glycaemic goals)	Fixed regimen (prandial insulin)	Increase TDD by 2 U/day
	Adjustable regimen (prandial insulin)	
	FPG >180 mg/dL	Increase TDD by 4 U
	FPG 140-180 mg/dL	Increase TDD by 2 U
	FPG 110-139 mg/dL	Increase TDD by 1U
	2-h PPG or next premeal glucose >180 mg/dL	Increase prandial dose for the next meal by 10%
	Premixed insulin	
	FPG/premeal BG >180 mg/dL	Increase TDD by 10%
Step3: Monitor for hypoglycemia	Fasting hypoglycemia	Reduce basal insulin dose
	Night time hypoglycemia	Reduce basal insulin or reduce short/rapid-acting insulin taken before supper or evening snack
	Between meal hypoglycemia	Reduce previous premeal short/rapid-acting insulin

*Basal + prandial insulin analogs preferred over NPH + regular insulin or premixed insulin, #For most patients with T2D taking insulin, glucose goals are HbA1c <7% and fasting and premeal BG <110 mg/dL in the absence of hypoglycemia. HbA1c and FPG targets may be adjusted based on the patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk. BG: Blood glucose, FPG: Fasting plasma glucose, NPH: Neutral protamine Hagedorn, 2-h PPG: 2-h postprandial glucose, TDD: Total daily dose, FPG: Fasting plasma glucose, T2D: Type 2 diabetes,
HbA1c: Glycosylated hemoglobin

INDIVIDUALIZING THERAPIES AND PRECISION DIABETOLOGY

ABCD (EFGH) approach for diabetes management Choice of any OAD agent should consider the patient's general health status and associated medical disorders. This patient-centric approach may be referred to as the ABCD (EFGH) approach for diabetes management. For any T2DM patients, the first line of therapy should be metformin unless it is not tolerated by the patient or contraindicated.

Individualized treatment

- For patients diagnosed with diabetes, consider a combination of metformin and one of the treatment options based on patient's age, BMI, CKD, duration of diabetes, established CVD, financial condition, glycemic status, and hypoglycemia risk.
- Drug choice should be based on patient preference, presence or absence of various comorbidities and complications, and drug characteristics to reduce glucose levels while minimizing side effects, especially hypoglycemia and weight gain.
- A comparative effectiveness meta-analysis suggests that most available non-insulin agents added to metformin therapy lower HbA1c around 0.9-1.1%[271]. In contrast, all oral antidiabetic agents and GLP-1 RA can reduce HbA1c by 0.5–2.0% insulin can reduce HbA1c even up to 3.5% when used as monotherapy.[272]

Age

- DPP-4 inhibitors may be a suitable addition to metformin for elderly patients (≥ 65 years) as there is very low risk of hypoglycemia and weight gain; however, the dosage should be adjusted as per eGFR.[273] Recent RCTs have reported that gliptins are efficacious and safe with minimal side effects when used as add-on therapy in elderly patients with T2DM.[274–277]
- AGIs could also be a good choice for elderly patients. These agents have modest efficacy (A1c ↓ ~ 0.5%) and do not cause hypoglycemia. The major limiting factor for their use is the gastrointestinal side-effects, such as flatulence and diarrhoea[278]. A double-blind RCT revealed that the addition of acarbose improved the glycemic profile and insulin sensitivity in elderly patients with T2DM. AGIs were also proven to be more useful especially in terms of Glycemic reduction in Asians because of high carb intake as seen in the mentioned STARCH study as well. [279]
- The use of glitazones is restricted in elderly T2DM patients owing to the anticipated complications like weight gain, fluid retention, peripheral oedema, lens-oedema, aggravation of congestive heart failure, and osteoporosis in post-menopausal women. Newer SUs like extended-release formulations of low doses of Gliclazide and low-dose glimepiride due to their low risk of hypoglycemia can be safely used in elderly patients with T2DM.[280,281]
- Evidence regarding the use of GLP-1 RA and SGLT2i in elderly T2DM patients has emerged recently. These classes provide good glycemic control in patients with T2DM and can reduce CV risk. However, certain drawbacks such as cost, discomfort of injection and weight loss with GLP-1 RA, and increased risk of genital mycotic infections and urinary tract infections, hypovolemia, postural hypotension, euglycemic ketoacidosis, and weight loss with SGLT2i may limit their usage in some frail elderly T2DM patients.[281]
- Evidence suggests that basal insulin analogues such as glargine, detemir and degludec are effective and safe with less risk of hypoglycemia and weight gain compared to NPH or Premix insulins.[282,283] Moreover a pooled analysis from RCTs revealed that addition of modern insulin analogues to oral antidiabetic drugs in older adults was effective with regards to lower risk of hypoglycemia compared to NPH insulin.[284]
- Individualization of therapy is highly desirable based on risk of hypoglycemia, comorbidities, functionality, cost, and personal preference in elderly people with diabetes.

Body mass index

- While prescribing pharmacological treatments for overweight or obese patients with T2DM, one should first consider anti-diabetic medications which cause either weight loss or weight neutrality. GLP- 1 RA and SGLT2i are associated with weight loss. DPP-4 inhibitors and AGIs appear to be weight neutral while Glitazones, Sus, and insulin can lead to weight gain.[285,286] A systematic review and meta-analysis of 62 randomized trials revealed that, when compared to other antidiabetic agents, SGLT2i and GLP-1 RA were associated with clinically significant body weight loss (range, 1.2–2.3 kg) as add-on to metformin.[287]
- GLP-1 RA and/or SGLT2i seem to be the best add on therapy for those having high BMI. These groups of medications has highest weight reducing property in addition to excellent efficacy. A recent systematic review and meta-analysis reported that GLP-1 RA are associated with weight loss (–1.62 kg to –1.01 kg) in overweight or obese patients with T2DM with no difference in weight loss between different types of GLP-1 RA.[288]
- SGLT2i also has a weight reduction property. Evidence suggests that SGLT2i were associated with weight loss in patients with T2DM.[289,290] Agents of this class have an additional advantage that they can be given orally. However, a careful consideration should be given to possible taken with regards to known side effects such as recurrent genital infections, postural hypotension, and dehydration.
- DPP4 inhibitors are weight neutral and thus can be used as the second or third line of antidiabetic agents.[291,292] As some Gliptins like Sitagliptin and Vildagliptin having gone off patent, the prices of these agents have dropped making them more affordable. In addition, DPP4i are shown to be more effective in Asians in general and Indians in particular.[293,294, 295]
- Agents such as teneligliptin which are used exclusively in India led to significant and clinically meaningful reductions in HbA1c and PPG in Indian patients with T2DM.[296]
- Use of newer SUs such as gliclazide MR and Glimepiride do not result in significant weight gain in patients with T2DM unlike the older SUs.[297–299]
- Lean patients with T2DM with low-normal body mass index (<18). are a distinct group of patients which are common in India. These patients are usually younger age at onset, lower insulin reserve and hence have greater need for insulin.[300]

In those with diabetic kidney disease (CKD)

In patients with renal impairment, preference of therapy would be SGLT2i or DPP4i as add on therapy with metformin. Some DPP4i need dose adjustment as per eGFR; linagliptin and teneligliptin do not require any dose adjustment in renal disease.[301–304]

- Repaglinide is another agent which may be used across all stages of renal insufficiency. Use of pioglitazone is restricted in CKD; due to the risk of fluid retention and congestive heart failure (CCF).[305,306]
- Short acting SUs like glipizide and gliclazide are preferred in patients with moderate/severe renal impairment. Furthermore, in mild/moderate renal impairment, gliclazide MR and glimepiride can also be used, preferably at lower doses.[280.] However, in general, SUs are better avoided in renal impairment.

- Although GLP-1 RA, especially liraglutide, dulaglutide and oral semaglutide are recommended up to eGFR 15 ml/min, owing to their GI adverse effect, their use in renal insufficiency patients is limited.[305]
- AGIs can be used in patients with mild to moderate renal disease (eGFF>30 ml/min).[306]
- Insulin can be used in any stage of renal insufficiency. Insulin analogues are preferred over conventional insulins,[307] however, insulin doses may require reduction with falling eGFR and HbA1c targets also have also to be individualised.[308,309]
- *Refer to CKD section for use of SGLT2i in patients with CKD.*

Duration of diabetes

- Patients with long-standing T2DM are difficult to treat because these patients often lack sufficient β-cell function to respond to secretagogues. Additionally, they may have other comorbidities, including renal impairment.[310]
- Insulins are often used in patients with long-standing diabetes to address insulinopenic states.[311]
- Incretin-based therapies, particularly GLP-1 RA, also lower HbA1c significantly and have lower risks of hypoglycemia than insulin.[311]
- SGLT2i may also be useful as add on agent due to their insulin independent action.[312]
- AGI's can be also effective sometime owing to their beta- cell independent actions.

Established cardiovascular diseases

- The UKPDS showed that intensive glycaemic control can reduce microvascular complications and to some extent CVD risk in patients with T2DM.[313]
- In patients with established CVD, GLP-1 RA and SGLT 2i with proven efficacy may be preferred.[314–320]
- In patients with heart failure and CKD, SGLT2i or GLP-1 RA may be preferred unless contraindicated.[314,315,319,321]
- Pioglitazone has been shown in few studies to reduce CVD risk,[322,323] however, it should not be used in patients with heart failure[324] or those with low ejection fraction.[325]
- Glimepiride or Gliclazide MR is preferred over conventional sulfonylureas in patients at increased risk of CVD or with established CVD.[280,326,327]
- AGIs have demonstrated CV Risk reduction by reducing Inflammation & post prandial hyperglycemia so could be a good option in these pts with ASCVD after Metformin.

Financial concern

- Considering that many Indian patients have to pay for their treatment and OPD visits out of their pocket and the treatment also needs to be continued lifelong, cost of therapy also plays a crucial role in T2DM patients from the Indian subcontinent.
- Sulphonylureas can be a good addition to metformin considering their cost, particularly in the light of the recent CAROLINA trial demonstrating the CV neutrality of glimepiride compared to linagliptin.[326] Pioglitazone or inexpensive DPP-4 inhibitors or SGLT2i can also be considered when combinations of SUs and metformin cannot achieve the desired target. Conventional insulin can be used at any stage considering its efficacy and cost.

Glycemic status

- The order of glucose-lowering agents according to their efficacy of HbA1c reduction are insulin, SUs, Metformin, GLP-1 agonists, SGLT2i, pioglitazone, DPP-4 inhibitors, glinides and AGIs.[272,328–330]

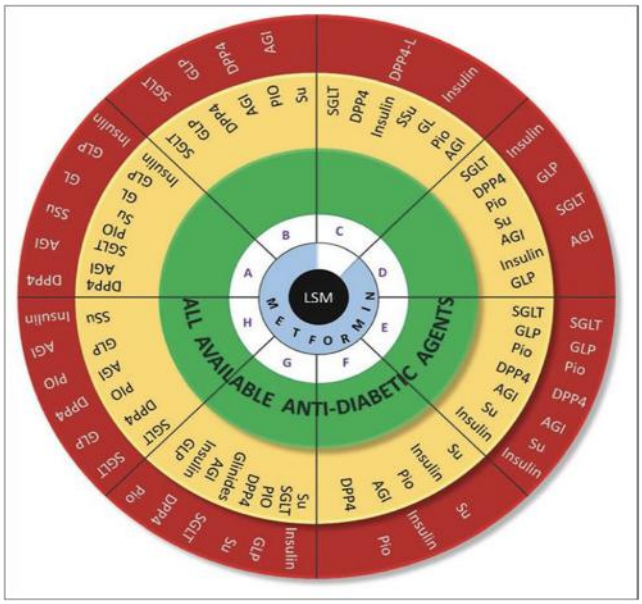
Hypoglycemia concern

- Hypoglycemia is an important limiting factor during treatment course of diabetes while targeting good glycemic control.
- Insulins, Sulfonylureas and glinides have an increased risk of moderate to severe hypoglycemia compared with other classes of agents in monotherapy.[328,331]
- While initiating DPP-4 inhibitor on a background of secretagogues such as SUs, the dose of SUs needs to be reduced and close monitoring of blood glucose is necessary.[332,333] Similarly, while initiating SGLT2i on a background of insulin or secretagogues, the dose of insulin or secretagogues needs to be reduced.[333]
- In patients with a history of hypoglycemia or for those at high risk of hypoglycemia, GLP-1 agonists or SGLT2i or DPP-4 inhibitors or AGIs or pioglitazone should be considered as first choice with metformin.[334]
- Patients prone to hypoglycemia should not preferably be put on glinides, SUs or insulin, since there are greater chances of hypoglycemia with these agents.
- Individuals in whom hypoglycemia further poses risk include:
- Patients with established cardiovascular disease
- Elderly patients
- Patients suffering from CKD and those who cannot perform SMBG without the help of others
- Patients who stay alone, especially in remote areas
- Patients with shortened life expectancy
- Patients having documented hypoglycemia unawareness
- Autonomic neuropathy

Implementations

The health impact of T2DM is well known, and its management has substantial effects on individual and societal health, psychological well-being, quality of life, and economic repercussions. Clinical practice recommendations in diabetes management are tools for healthcare providers that can ultimately improve health across populations; however, for improved outcomes, diabetes care must also be individualized for each patient. There is no 'one-size-fits-all' treatment for patients with T2DM, and diabetes management should be individualized. The ADA also highlights the importance of patient-centered care, which is respectful of and responsive to individual patient preferences, needs, and values and ensures that the patient is involved in all clinical decisions.[335] An individualized therapy for T2DM could serve as a "real-world" approach, providing care that is responsive to individuals' specific and unique needs, preferences, and values, and also helping to combat adverse long-term outcomes.

RSSDI Therapeutic Wheel



From innermost to outermost:
A - Age = Advancing age
B - BMI = Increasing BMI
C - CKD = Advancing CKD
D - Duration of Diabetes = Increasing duration
E - Established CVD = Low CVD risk to Established CVD risk
F - Finance = Adequate to Limted
G - Glycemic Status = Worsening glycemia control
H - Hypoglycemia = Hypoglycemia concern

AGI, Alpha-glucosidase inhibitor; DPP4, Dipeptidyl Peptidase-4 (DPP 4) Inhibitors; DPP4-L, Dipeptidyl Peptidase-4 Inhibitors-Linagliptin; GL, Glinides; GLP, Glucagon-like peptide-1 receptor agonist; PIO, Pioglitazone; SGLT, Sodium-glucose Cotransporter 2 Inhibitors; SSu, short acting sulphonylureas; Su, Sulphonylurea; LSM, lifestyle modification

Note: Hierarchy of therapy is depicted in clock-wise manner
GLPs must be used based on costs. Any of the drugs can be used in the green. For other zones, drugs must be used in the given order.

POSTPRANDIAL HYPERGLYCEMIA

Recommendations

Recommended Care

- Postprandial hyperglycemia is defined as having postprandial glucose level higher than the target after a usual meal and on medications (if any).
- PPG should be measured 2-h after the start of a usual meal and medications (if any).
- Target PPG: 160 mg/dL as long as hypoglycemia is avoided.
- Both non-pharmacologic and pharmacologic therapies should be considered
  - MNT: diet with low glycemic load is recommended
  - AGIs (acarbose, miglitol or voglibose), DPP4 inhibitors, SGLT2 inhibitors or GLP-1 analogues (preferably short-acting) as the first add-on to metformin therapy
  - Glinides and short-acting sulfonylureas as alternative options
  - Rapid-acting insulin analogues may be considered over regular insulin when postprandial hyperglycemia is a concern, especially when the risk of hypoglycemia is high.
- Combination therapy of AGI with other agents may be considered.
- SMBG should be considered as it is the most practical method for monitoring postprandial glycemia.
- Efficacy of treatment regimens should be monitored frequently to guide therapy towards achieving PPG targets.
- Glycemic Index, as well as dietary insulin index of food items, may be considered for better PPG control.

Background

Patients with poorly controlled diabetes frequently develop micro-and macro-vascular complications. Evidence from extensive controlled clinical studies suggests that intensive glycemic control can significantly reduce their risk of development and/or progression[336–340]. Until recently, the predominant focus of diabetes treatment has been on lowering HbA1c levels, with emphasis on FPG[341,342]. However, control of fasting hyperglycemia alone is insufficient to obtain optimal glycemic control as evidence suggests that reducing PPG excursion is essential or perhaps more important for achieving desired glycemic targets[343]. It is understood that HbA1c is primarily impacted by FPG when it is away from the target. As it comes closer to the target, PPG starts taking the upper hand and contributes predominantly. Therefore, patients who achieved 2-h PPG within the reference limit will better accomplish target HbA1c values than those who realized FPG within the recommended range[344]. In Indians, the PPG remains relatively high across the HbA1c spectrum and very high even at higher HbA1c values[345–347]. The relative contribution of postprandial hyperglycemia to HbA1c levels in patients with T2DM is higher than FPG levels when HbA1c is <7.5%, decreasing progressively as HbA1c levels increase[348]. Therefore, targeting PPG and FPG is ideal for achieving optimal glycemic control. The purpose of these recommendations is to assist clinicians in developing strategies to consider and effectively manage post-meal glucose in people with T2DM in Asian countries.

Considerations

India has a high prevalence of diabetes, and the onset of diabetes is a decade early. Postprandial hyperglycemia is more prominent in Indians due to traditional high diets with the high glycemic index. Literature is limited regarding postprandial hyperglycemia despite its substantial role in micro-and macro-vascular complications.

Rationale And Evidence

Definition of postprandial hyperglycemia

- ADA 2019 and the IDF 2018 define postprandial hyperglycemia as a 2-h plasma glucose level of >200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT). It recommends using glucose load equivalent to 75 g of anhydrous glucose dissolved in water as prescribed by WHO[273,349].
- Asian Indians displayed a marked rise in prandial glucose excursion after consumption of 75 g of bread meal compared to their Caucasian counterparts[350,351].
- Elevations in PPG are due to decreased first-phase insulin secretion, reduced insulin sensitivity in peripheral tissues, and consequently decreased suppression of hepatic glucose output after meals, unsuppressed glucagon levels, and deficiency of intestinal incretin hormones GLP-1 and (glucose-dependent insulinotropic polypeptide) GIP[341].
- The causes of postprandial hyperglycemia are influenced by many factors, including a rapid flux of glucose from the gut, impaired insulin release, endogenous glucose production by the liver, and peripheral IR[352].
- Recent evidence suggests that the value of glycemia at 1-h during an OGTT is a stronger predictor of developing diabetes than the value at 2-h[353–355]. Therefore, in clinical practice, targeting PPG at 1-h instead of 2-h could significantly reduce the risk for CVD. The 1-h PPG has been correlated with increased left ventricular mass, left ventricular diastolic dysfunction, and carotid intima-media thickness (CIMT)[356–359]. However, measurement of plasma glucose after 1 hour of glucose load was higher than 2-hour value and correlated better with hepatic fat in non-diabetic obese adults.[360]
- Evidence from an Indian study based on patients with a history of T2DM for more than 25 years suggests that postprandial hyperglycemia was associated with an increased risk of diabetic nephropathy and neuropathy[345,361]. And Kumamoto's study suggested reductions in retinopathy and nephropathy with reduced PPG [Figure].[340,362]

• Elderly patients on SU were randomized to continue with SU or repaglinide. After 16 weeks, Glycated Albumin and GA/HbA1c ratio was improved in repaglinide recipients. [363]

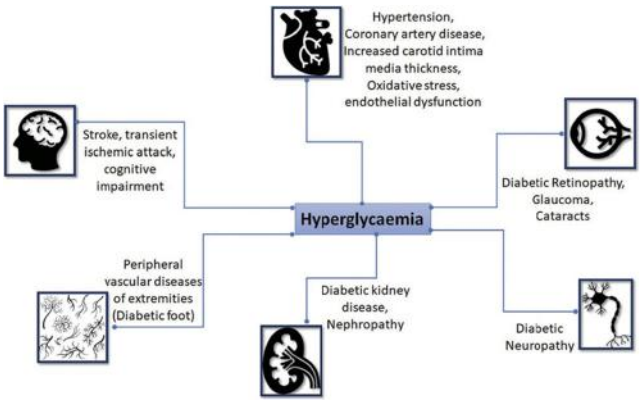


Figure 4: Secondary complications of postprandial hyperglycemia[364,365]

Addressing postprandial hyperglycemia

The HEART2D (Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus) and the NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) study could demonstrate the direct benefit of lowering postprandial hyperglycemia in reducing CVD in patients with T2DM.[366–368] However, emerging evidence indicates that agents that target PPG show significant positive trends in risk reduction for all selected CV events. Findings from the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial highlight that treating people with IGT with acarbose significantly reduced the risk of CVD and hypertension.[369] The Acarbose Cardiovascular Evaluation (ACE) trial highlighted that there was no significant impact of acarbose therapy in reducing the risk of major CV events. However, the incidence of diabetes was reduced, which may mitigate cardiovascular risk in the longer term by delaying the onset of T2DM in the high-risk population.[370]

Postprandial hyperglycemia is an important pathophysiological state contributing to the several secondary complications including CV events. Management of postprandial hyperglycemia is central to long-term glycemic control and an essential part of CVD prevention T2DM. Therefore, it should be routinely monitored in T2DM patients using 2-h post-meal. Thus, screening for prediabetes and monitoring the glycemic control in patients with T2DM should include PPG as a predictive marker for all-cause premature death, CV risks, and FPG and HbA1c levels.[370–372] The level of implementation of routine screening for post-meal hyperglycemia, using the OGTT, should be improved in the Asia-Pacific region, combined with broader use of effective interventions to manage postprandial hyperglycemia.[373]

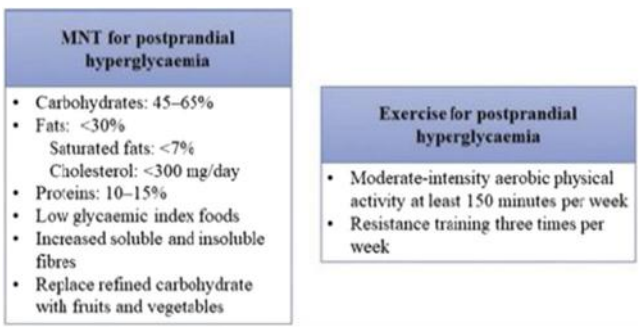


Figure 5: MNT to prevent postprandial hyperglycemia. (MNT: Medical nutrition therapy)

Strategies to prevent postprandial hyperglycemia

Non-pharmacological

• Physical activity and MNT [Figure] are the cornerstones of non-pharmacologic therapy in T2DM patients.[362]

• A randomized crossover study showed that in T2DM patients, walking after meals is more effective for lowering postprandial glycaemia.[374]

• Traditional Asian Indian and Chinese diets are carbohydrate-rich (as high as 80% of the macronutrient composition) with high glycemic index values.[375] Consumption of rice is very high in South India, which is associated with a 4–5 fold increase in the risk of diabetes.[376] The higher carbohydrate load in the Indian diet leads to greater PPG excursion, increased glucosidase and incretin activity in the gut, which leads to higher lipemic peaks and associated CVD.[375] Evidence suggests that diets with low glycemic index values are beneficial in controlling postprandial hyperglycemia.[341,377,378] On the other hand, bean-based breakfast was associated with fewer glycemic excursions throughout the day compared to rice-based breakfast, which is predominant in most parts of India and Asia.[379] *For details, please refer to the MNT and lifestyle section*

• Focusing on carb counting is not sufficient for controlling pp sugar. Protein and fat content also play a role in augmenting insulin secretion. The dietary insulin index should be utilized for glycemic management.[380]

Pharmacological

• Based on limited Indian evidence available from literature, the panel relied on expert opinion for pharmacological management of postprandial hyperglycemia, which includes the following:

- GLP-1 analogues are effective in controlling postprandial glucose either when used in association with metformin or part of a combination therapy including basal insulin. The short acting GLP-1 agonists (exenatide and lixisenatide) are preferred when isolated postprandial hyperglycemia is present.
- The ultrafast acting insulin analogue has demonstrated significant benefits in reducing 1-h PPG following mealtime administration.
- DPP-4 inhibitors have shown significant benefits in reducing PPG excursions and lowering HbA1c.
- Use of glinides is limited to the treatment of postprandial hyperglycemia only if sulfonylureas are contraindicated, or economic consideration prohibits the use of newer and expensive agents.
- AGIs (acarbose, miglitol, and voglibose) can be used as a first-line drug in early T2DM and in combination with nearly all established OADs and insulin. Moreover, AGIs tend to inhibit carbohydrate absorption from the gut which can be of particular importance in Indian settings where there are increased odds for PPG and lipid excursion due to consumption of diets with the high glycemic index. In a prospective randomized trial on T2DM from five centers across Korea, patients were inadequately controlled on Metformin + Sitagliptin, acarbose was added as 2nd add-on. Acarbose was found to be a safe and effective add-on to Metformin + Sitagliptin for improving glycemic parameters.[381]

Implementation

Frequent monitoring of glucose levels using techniques such as SMBG can significantly improve glycemic control besides detecting PPG excursion. SMBG is currently the optimal method for assessing plasma glucose levels. Evidence suggests that structured SMBG followed by therapeutic interventions results in more significant HbA1c reduction in individuals with T2DM compared with programs without structured SMBG.[382–384] Therefore, the panel suggests including SMBG with appropriate patient education for optimal management of post-meal hyperglycemia. Although, SMBG estimates the average glucose accurately, it underestimates the glucose excursions. A continuous glucose monitoring system (CGMS) provides information on glucose levels, patterns and trends,

reflecting the effects of medication, meals, stress, exercise, and other factors that affect glucose levels. The CGMS could also be a useful method to detect postprandial hyperglycemia and to improve therapeutics management in patients with T2DM.[347,385–387]

ACUTE METABOLIC COMPLICATIONS

Hyperglycemic Crisis (Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State)

Recommendations

Recommended Care

- Treatment individualization based on careful clinical and laboratory assessment is needed.
- Management goals should include:
  - Restoration of circulatory volume and tissue perfusion
  - Correction of electrolyte imbalance and reversal of ketosis
  - Resolution of hyperglycemia
  - Identification and prompt treatment of precipitating events
  - Avoiding complications of therapy, particularly cerebral oedema
  - Prevention of recurrent episodes
- Meticulous monitoring of clinical and biochemical responses using a flow chart is essential to document hour-by-hour clinical observations, intravenous and oral medications, fluids, and laboratory results.
- Admission to an intensive care unit or comparable setting with adequately trained nursing and medical staff and 24 h laboratory services for frequent monitoring is warranted for children <2 years of age and in case of compromised circulation, coma, and risk of cerebral edema.
- Emergency assessment should follow the general guidelines of advanced life support, with particular attention to airway and breathing patterns, the severity of dehydration, mental status, source of infection, level of consciousness (Glasgow coma scale), and frequent monitoring of clinical and laboratory parameters.
- If laboratory measurement of serum potassium is delayed, perform an electrocardiogram for baseline evaluation of potassium status. A cardiac monitor should be used for continuous electrocardiographic monitoring to assess T waves for evidence of hyper-or hypo-kalemia and arrhythmias.
- In the unconscious or severely obtund patient, secure the airway and empty the stomach by continuous nasogastric suction to prevent pulmonary aspiration.
- Fluid replacement should begin before starting insulin therapy to restore peripheral circulation.
- Adequate oxygenation should be maintained using supplemental oxygen to patients with severe circulatory impairment or shock.
- Give antibiotics to febrile patients after obtaining appropriate cultures of body fluids.
- The rate of fluid administration should not exceed 1.5-2 times the usual daily maintenance requirements.
- Insulin administration should begin 1-2 h after starting fluid replacement therapy.
- In critically ill and mentally obtunded patients, continuous intravenous insulin is the standard of care.
- Bicarbonate administration is not recommended except for the treatment of life-threatening hyperkalemia. Patients with multiple risk factors for cerebral edema, have mannitol or hypertonic saline at the bedside, and the dose should be calculated beforehand. If neurologic status deteriorates acutely, hyperosmolar therapy should be given immediately.

Background

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) represents the most common and severe acute metabolic complications of diabetes. Despite well-developed diagnostic criteria and treatment protocols, DKA and HHS are associated with substantial morbidity and mortality.[388] The overall DKA mortality recorded is <1%, but a higher rate is reported among patients aged >60 years and individuals with concomitant life-threatening illnesses.[388–390] HHS typically occurs in older patients with T2DM with an intercurrent disease such as infection, surgery, or ischemic events and is associated with a higher mortality rate than DKA. The mortality rate with HHS is almost 10-fold more elevated when compared with DKA.[391–393]

Pathogenesis of these life-threatening hyperglycemic emergencies is related to absolute, or relative insulin deficiency and an increase in insulin counter-regulatory hormones that lead to altered metabolism of carbohydrate, protein, and fat and varying degrees of osmotic diuresis and

Table 11: Diagnostic criteria for diabetic ketoacidosis and hyperglycemic hyperosmolar state

Measure	DKA	HHS
Plasma glucose level (mg/dL)	>250	>600
Arterial or venous pH	<7.30	>7.30
Serum bicarbonate level (mmol/L)	<15	>15
Urine or blood ketones	Positive	Negative or low
Urine or blood βhydroxybutyrate (mmol/L)	≥3	<3
Effective serum osmolality (mOsm/kg)	Variable	>320
Anion gap (mmol/L)	>12	<12
nitroprusside reaction method, defined as 2[measured Na^+ (mEq/L)] + glucose (mg/dL)/18, Canion gap: (Na^+) - [(Cl^- + HCO - (mEq/L)]. 3		

DKA: Diabetic ketoacidosis, HHS: Hyperglycemic hyperosmolar state

Dehydration, ketosis, and acidosis[394] termed together as decompensated diabetes, the prevalence and mortality for DKA and HHS remain indistinct across various age, gender, and racial groups of hospitalized diabetics. If not interrupted by exogenous insulin, fluid, and electrolyte therapy, it would lead to fatal dehydration, hypoperfusion, and ultimately metabolic acidosis.

In DKA, insulin deficiency and ketoacidosis are the prominent features of the clinical presentation, and insulin therapy is the cornerstone of therapy [Tables 9 and 10]. Severe hyperglycemia, osmotic diuresis, and dehydration with altered mental status without significant acidosis characterize HHS. Fluid replacement remains the cornerstone of therapy for HHS. A considerable overlap has been reported in more than one-third of patients exhibiting mixed DKA and HHS features [Table #]. Because the three-pronged approach to therapy for either DKA or HHS consists of fluid administration, intravenous insulin infusion, and electrolyte replacement, and mixed cases are managed using the same method. ICU admission is indicated in the management of DKA, HHS, and diverse patients in the presence of cardiovascular instability, inability to protect the airway, obtundation, the presence of acute abdominal signs or symptoms suggestive of acute gastric dilatation, or if there is not adequate capacity on the floor unit to administer the intravenous insulin infusion and to provide the frequent and necessary monitoring that must accompany its use [Figure 6 and Table 13].

Considerations

Treatment of patients with DKA and HHS is associated with substantial mortality and healthcare costs. In a developing country like India, due to poor socio-economic status, many patients with T2DM tend to have poor compliance and poor glycemic control. Thus any precipitating factor manages to land them in a state of hyperglycemic emergencies, including DKA and HHS.

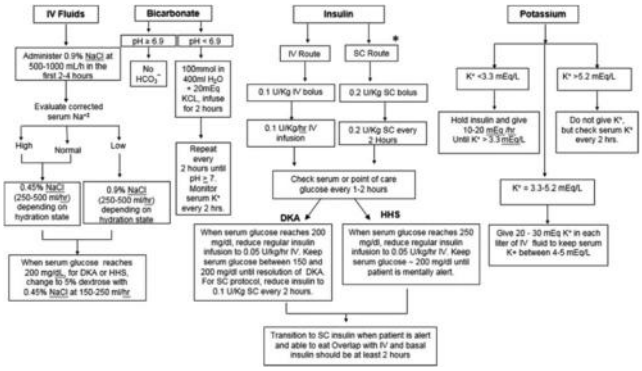


Figure 6: Algorithm for the management of DKA and HHS. DKA: Diabetic ketoacidosis; HHS: Hyperglycemic hyperosmolar state; IV: Intravenous; SC: Subcutaneous

Table 12: Monitoring of clinical signs and biochemical investigations

Plasma glucose and HbA1c levels	Venous pH
BUN, creatinine, electrolytes (including bicarbonates) with a calculated anion gap, and hematocrit	Fluid input and output
Serum osmolality	Vital signs (heart rate, respiratory rate, BP)
Serum and urinary ketones	Neurological observations for warning signs and symptoms of cerebral edema
Arterial blood gases	ECG, chest X-ray, USG abdomen and pelvis
USG: Ultrasound, BUN: Blood urea nitrogen, ECG: Electrocardiogram, BP: Blood pressure, HbA1c: Glycosylated hemoglobin	

Table 13: Management of acute metabolic complications

Fluid replacement therapy
In the absence of cardiac compromise, isotonic saline (0.9% NaCl) is infused at a rate of 15-20 mL/kg/h or 1-2 l over 1-2 h for prompt recovery of hypotension and/or hypoperfusion
Continue with 0.9% NaCl at a similar rate if patient is hyponatremic or switch to 0.45% NaCl infused at 250-500 mL/h if the corrected serum sodium is normal (eunatremia) or elevated (hypernatremia)
When plasma glucose level is <200 mg/dL, change to 5% dextrose in saline as long as the insulin infusion continues.
Insulin therapy
Start insulin infusion 1-2 h after starting fluid replacement therapy (after initial volume expansion), and serum potassium restored to>3.3 mEq/l
A regular human insulin IV bolus of 0.1-0.15 U/kg followed by continuous insulin infusion at 0.1 U/kg/h
IV bolus is avoided in children as it may increase the risk of cerebral edema and can exacerbate hypokalemia.
When glucose level reaches 200 mg/dL in DKA or 300 mg/dl in HHS, reduce insulin rate to 0.02-0.05 U/kg/h. After that, adjust the rate to maintain a glucose level of 150-200 mg/dL in DKA and 250-300 mg/dL in HHS
Continue insulin infusion until resolution of ketoacidosis
Subcutaneous rapid-acting insulin analogs (lispro and aspart) every 1-2 h. might be an alternative to IV insulin in patients with mild to moderate DKA
Initial dose subcutaneous: 0.3 U/Kg, followed one h later at 0.1 U/Kg every one h, or 0.15-0.2 U/kg every two h
Potassium replacement
If the patient is hypokalemic, start potassium replacement at the initial volume expansion and before starting insulin therapy. Otherwise, begin after initial volume expansion and concurrent with insulin therapy.
With initial rapid volume expansion, a concentration of 20 mmol/l should be used.
The maximum recommended rate is 0.5 mmol/kg/h.
The treatment goal is to maintain serum potassium levels of 4-5 mEq/l.
Bicarbonate therapy
Not routinely recommended; only indicated in adults with severe acidosis with pH <6.9
If pH <6.9, consider 100 mmol (2 ampules) in 400 ml sterile water with 20 mEq KCI administered at a rate of 200 ml/h for two h.until pH is ≥7.0.
If the pH is still <7.0 after this is infused, we recommend repeating the infusion every two h. until pH reaches >7.0.
Transition to subcutaneous insulin
To prevent recurrence of ketoacidosis or rebound hyperglycemia, consider the overlap of IV insulin for 15-30 min (with rapid-acting insulin) or 1-2 h (with regular insulin) or longer (with intermediate or long-acting insulin) after subcutaneous insulin is given.
The most convenient time to change to subcutaneous insulin is just before mealtime.
For patients treated with insulin before admission, restart previous insulin.
Regimen and adjust dosage as needed.
For patients with newly diagnosed DM, start the total daily insulin dose at 0.5-0.8 U/kg/day. Consider multi-dose insulin given as a basal and prandial regimen.
SGLT2i: avoid permanently.
DKA: Diabetic ketoacidosis, HHS: Hyperosmolar hyperglycemic state, IV: Intravenous, DM: Diabetes mellitus.

HYPOGLYCEMIA

Recommendations

Recommended Care

- The risk of hypoglycemia should be assessed during every visit in patients with T2DM by using questionnaires.
- The patient should be well educated and informed regarding:
  - The symptoms, causes, and risks associated with hypoglycemia
  - Usage of SMBG tools with frequent monitoring, especially for patients taking insulin
  - Insulin dose adjustment considering blood glucose values
- Strict monitoring of hypoglycemic episodes is recommended for patients taking insulin, sulfonylureas, or meglitinides alone or in combination.
- Modern insulins or sulfonylureas should be used instead of traditional drugs in patients with a high risk of hypoglycemia.
- Oral glucose (15-20 g) is preferred in conscious hypoglycemic patients (glucose alert value of <70 mg/dL). Repeat the treatment if SMBG shows persistent hypoglycemia after 15 min. The patient should consume a meal or snack once SMBG returns to normal to prevent the recurrence of hypoglycemia
- Intramuscular glucagon or intravenous glucose is preferred for unconscious patients or patients with clinically significant hypoglycemia (glucose alert value <54 mg/dL). Repeat intramuscular or subcutaneous glucagon dose of 0.5 mg if there is no symptomatic improvement.
- Glucagon is to be avoided in patients with sulfonylurea-induced hypoglycemia.
- Treatment should be modified in the event of hypoglycemia repeatedly occurring at a particular time of the day or in the event of hypoglycemia unawareness.
- Hypoglycemia occurring in the setting of advanced kidney disease (CKD stage 4 or 5 requires relatively longer observation for the avoidance of recurrence even long after initial corrective measures are taken.

Limited Care

- All patients with risk of hypoglycemia should be enquired about symptomatic and asymptomatic hypoglycemia at each visit.
- Patients and their family members should be well educated about the identification and management of hypoglycemia, especially night-time hypoglycemia.
- Hypoglycemia should be strictly managed and monitored in special situations such as the elderly, pregnancy, fasting, and metabolic disorders.

Background

Hypoglycemia is a significant cause of concern with some antidiabetic drugs during glycemic management in patients with T2DM.[395] However, the extent of hypoglycemia varies with different antidiabetic drugs' pharmacokinetic and pharmacodynamic properties. The International Hypoglycemia Study Group categorizes hypoglycemia into three categories based on the glycemic criteria.[396]

- Glucose alert value (level 1): <70 mg/dL (3.9 mmol/L)
- Clinically significant hypoglycemia (level 2): <54 mg/dL (3.0 mmol/L)
- Severe hypoglycemia (level 3): no specific glucose threshold.

The prevalence of hypoglycemia in patients with T2DM in India is relatively high. A recent cross-sectional study reports that nearly 96% of patients (out of 366 patients) were associated with at least one or other symptoms of hypoglycemia (dizziness, weakness). Furthermore, patients taking insulin in addition to OADs were at higher risk than patients taking OADs alone (OR, 2.3; p <0.01).[397] Meanwhile, another cross-sectional study including 1650 patients from South India revealed that the cumulative incidence of institutional hypoglycemia was 12.36%, among which 26.96% had asymptomatic episodes.[398] Severe hypoglycemia can lead to several diabetes-related short-and long-term complications such as neurocognitive dysfunction, retinal cell death, and loss of vision[399] and may lead to coma or death if not reversed.[395] The ACCORD and ADVANCE trials and other pieces of evidence reported that severe hypoglycemia was directly associated with mortality in patients with T2DM.[400–402] Furthermore, Kalra *et al*. stated that diabetes patients with severe hypoglycemia are associated with a sixfold increase in deaths over those not experiencing it.[399] Therefore, urgent steps must be taken with some corrective measures against hypoglycemia in T2DM patients to minimize the burden. Following are some causes and risk factors for hypoglycemia [Table 14].[399]

Considerations

Factors such as the intensity of hypoglycemic risk, patient characteristics, drug usage, fasting, and patient education should be considered while framing the recommendations for hypoglycemia management in patients with T2DM.

Table 14: Causes and risk factors for hypoglycemia [397,403]

Causes	Risk factors
Metabolic defects	Glucose-lowering drugs (especially SU/insulin)
Autoimmune conditions Dietary toxins	Increased glucose utilization or decreased glucose production
Alcohol consumption Stress Infections Starvation Severe excessive exercise	Female gender Inborn errors of metabolism Sleep Long duration of diabetes Extremes of age Progressive insulin deficiency
	Intensive glycemic control on OADs and insulin (alone or in combination)
	Skipping of meals
	DKD, hepatic impairment
	Cortisol Insufficiency
	Autonomic Failure
	Cognitive impairment
	Polypharmacy
	ACE and β-blockers

ACE: Angiotensin-converting-enzyme, DKD: Diabetic kidney disease, OADs: Oral antidiabetics, SU: Sulfonylureas

Rationale and Evidence

Identification

- Symptoms of hypoglycemia include but are not limited to excess sweating and hunger, dizziness, blackout, fainting, fatigue, light-headedness or shakiness, nausea or vomiting, mental confusion, unresponsiveness, and dryness or tingling lips.[395]
- Nocturnal hypoglycemia is suspected in night-time sweating, hunger, and anxiety. Nightmares, early morning headaches, and labile morning sugars should also alert the physician.[404,405]
- Some endocrinologists or diabetologists use a three-step approach (Whipple's Triad) to diagnose hypoglycemia. It includes:
  - Low blood glucose level
  - Symptoms of hypoglycemia at the time of the low glucose level
  - Symptom relief with the treatment of hypoglycemia.

Management

- Management of hypoglycemia can be subdivided into three aspects:
  - Prevention of hypoglycemia
  - Treatment of hypoglycemia
  - Adjustment or withdrawal or modification of current antidiabetic regimen.
- Glucagon in solution form is known to rapidly degrade to form β-sheet-rich amyloidogenic fibrils. The specific type of degradation products varies with time of exposure/aging, concentration, pH, shear, temperature, and presence of certain excipients. The generation of degradation

products presents two problems in the clinic: (i) loss of efficacy over time and (ii) potential cytotoxicity/neurotoxicity associated with amyloidogenic fibrils.[406]
- The ADA guides protocol to treat severe hypoglycemia treatment protocol; for conscious individuals with BG less than 70 mg/dL, 15 to 20 g of pure glucose is the preferred treatment, although any carbohydrate with glucose is appropriate. If the patient continues to be hypoglycemic 15 minutes after treatment, this treatment should be repeated. Once the patient is no longer hypoglycemic with a BG of 70 mg/dL or greater, the patient should consume a snack to prevent recurrent hypoglycemia. This is commonly known as the "15-15 rule". Because of its hypertonicity, administration of IV D 50 / 25 carries an increased risk of extravasation.[407]

Prevention of hypoglycemia
- Hypoglycemia prevention is preferable to treatment, as it is much more likely to avoid severe events and economic burdens.[408] Hypoglycemia prevention requires a combined effort from a physician and the patient. Patient education, patient counseling, and continuous blood glucose monitoring are the critical factors that need to be considered to prevent hypoglycemia in patients with diabetes. Evidence suggests that a proper and structured diabetes education helps in reducing diabetic complications, including hypoglycaemia.[409–412]
- Furthermore, interventions targeting health beliefs and attitudes about hypoglycemia and diabetes self-management can be more effective than knowledge-centered patient education, focusing on symptom perception in reducing unawareness of hypoglycemia.[399] Patients receiving insulin for the treatment of T2DM can be benefitted by adjusting insulin doses following the SMBG procedure.[399–405,408–413] In addition, a cross-sectional study from India reports that 85% of patients were taking timely meals to prevent hypoglycaemia.[397] Stratifying patients according to age and avoiding very tight glucose control in elderly patients (>70 years) and very young children <5 years of age will help to prevent hypoglycemia in these high-risk people.

Adjustment or withdrawal, or modification of the ongoing antidiabetic regimen
- Most antidiabetic agents can produce hypoglycemia; however, the intensity depends upon their mechanism of action. Insulin, sulfonylureas, and meglitinides, due to their glucose-independent mechanism of action, cause a high risk of hypoglycemia.[399]
- The UK Hypoglycemia Study Group report that severe hypoglycemia increased from 7% to 25% in patients treated with insulin for <2 years and those treated for >5 years.[414] However, modern insulin analogs report a lower incidence of hypoglycemia than traditional human insulins.[415–417]
- Modern sulfonylureas like gliclazide MR and glimepiride are associated with lesser hypoglycemic episodes among all sulfonylureas.[418,419] Meglitinides were reported to inflict high rates of hypoglycemia.[420] In special situations like the elderly, fasting, metabolic disorders, and pregnancy, the dose of these drugs should be adjusted or modified to avoid further complications. Furthermore, avoid/reduce the insulin dose in people with CKD who tend to develop hypoglycemia.

Treatment of hypoglycemia
- 15 to 20 g of carbohydrates (four teaspoons of sugar or glucose) can be given orally to a conscious patient with hypoglycemia; if unconscious, glucagon injection intramuscularly or glucose injection intravenously can be preferred.[395–399]
- Glucagon to be avoided in sulfonylurea-induced hypoglycemia.
- Caretakers of hypoglycemia-prone diabetes patients (family members, roommates, school personnel, child-care providers, correctional institution staff, or co-workers) should be well instructed on using glucagon kits, including where the equipment is located and when and how to administer glucagon.[395]
- Acute glycemic response correlates better with the glucose content than with the carbohydrate content of food. Therefore, pure glucose is the preferred treatment.[345] Fifteen minutes after glucose administration, an SMBG should be done, and the treatment should be repeated if hypoglycemia persists. The patient should be advised to eat a regular meal or snack to prevent hypoglycemia recurrence.[421]

Implementations

Patient empowerment with hypoglycemia monitoring tools, hypoglycemia risk awareness, available preventive strategies, and a physician-patient collaboration treatment plan can reduce the frequency and intensity of hypoglycemia.

CHRONIC COMPLICATIONS 1: RETINOPATHY, NEUROPATHY, DIABETIC KIDNEY DISEASE

RETINOPATHY

Recommendations

Recommended Care
• Documentation of the formal history of vision and visual acuity, either by recording it on a sheet or electronic medical record (EMR) should be made mandatory first at the time of diagnosis and then periodically. • Ensure that examination of the eyes of people with T2DM is performed around the time of diagnosis and then routinely every 1-2 years as part of a formal recall process: - Measure and document visual acuity, corrected with glasses or pinhole - Record ocular pressure and assess the condition of the iris and lens - Assess retinopathy: » Using retinal photography through dilated pupils, performed by an appropriately trained healthcare professional, or » Through examination by an ophthalmologist • Discuss the reasons for an eye examination with the person with diabetes. • Counselling must include components on smoking, diet, alternative medicines, exercise, and appropriate choice of drugs for BP and Lipids. • Counsel women who are planning pregnancy on the risk of progression of retinopathy during pregnancy, especially if there is pre-existing retinopathy. • • Ensure regular follow-up throughout pregnancy and up to 1 year post-partum. • Use tropicamide to dilate pupils, unless contraindicated (rule out history of glaucoma), after discussing the implications and obtaining agreement of the person with diabetes. • Classify the findings of eye examination as required: routine review, earlier review or referral to an ophthalmologist (if not making the examination). • The following frequency of screening is suggested: - 1-2 years, if no retinopathy, depending on clinical situation - 12 months, if minimal unchanged retinopathy - 2-4 months, after any active ophthalmic intervention - 3-6 months, if worsening since last examination - More often during pregnancy

- The following situations require specialist referral:
  - The same day:
    - » Sudden loss of vision
    - » Evidence of retinal detachment
  - Within one week:
    - » Evidence of pre-retinal and/or vitreous hemorrhage
    - » New vessel formation or rubeosis iridis
    - » Inability to see or assess disc or fovea
    - » Raised ocular pressure
  - Within 1-2 months:
    - » Advanced retinal lesions (4:2:1 rule)
    - » Microaneurysms or retinal hemorrhages in 4 quadrants
    - » Venous beading in two quadrants
    - » IRMAs in one quadrant
    - » Unexplained deterioration of visual acuity
    - » Macular oedema
    - » Unexplained retinal findings
    - » Cataract
    - » Inability to visualize fundus
- Stepped approach should be adapted to manage hyperglycemia, as intensive glycemic control can cause transient (early) worsening of symptoms and even lead to cotton wool spots.
- GLP-1 agonists may initially worsen diabetic retinopathy, and hence must be used with caution.
- Advice that good control of blood glucose, BP and blood lipids, and cessation of smoking can help to reduce the risk of development or worsening of eye complications.
- Advice that DR is not a contraindication for use of aspirin, if this is indicated for prevention of CVD.
- Advise that tests of intra-ocular pressure should be done periodically.
- Explain guarded prognosis about regaining vision after intra-ocular lens (IOL) surgery in mature/hyper mature cataract because of poor assessment of retina in the presence of mature cataract.

  Discourage use of alternative medicines as they can cause further complications.

Limited Care

- Use direct fundoscopy through dilated pupils, performed by a healthcare team member who is adequately trained and has the appropriate experience to assess retinopathy.
- Check visual acuity.
- Repeat review, referral and preventative therapy areas for recommended care.
- Less-frequent examinations (every two years) may be considered following one or more normal eye examinations.
- Discourage the use of alternative medicines as they can cause further complications.

Background

Diabetic eye disease comprises a group of eye conditions that affect people with diabetes, such as diabetic retinopathy (DR), diabetic macular edema (DME), cataract, and glaucoma.

DR is a microvascular complication of diabetes and one of the leading causes of blindness or vision impairment in India[422,423]. It affects retinal blood vessels and is the most common cause of vision loss among people with diabetes and the leading cause of vision impairment and blindness among working-age adults.[424] Visual loss from DR could be due to diabetic macular edema (DME: swelling in the retinal macula) or proliferative diabetic retinopathy (PDR). Factors such as longer duration of diabetes and poorer glycemic and BP control were found to be strongly associated with DR.[425,426]

DR has also been linked to cardiovascular mortality in some cases.[427] In a cross-sectional study carried out by the All India Ophthalmological Society, the prevalence of DR was 21.7%, and the rate was high in men ($p=0.007$), in patients with diabetes duration>5 years ($p=0.001$), in patients with age>40 years ($p=0.01$), in insulin users ($p=0.001$), and in patients with a history of vascular accidents ($p=0.0014$)[422]. Furthermore, in the cross-sectional survey of Indian patients with T2DM in CINDI (chronic complications in newly diagnosed patients with type 2 diabetes mellitus in India) and CINDI2 (cardiovascular risk factors, micro and macrovascular complications at diagnosis in patients with young-onset type 2 diabetes in India), DR was prevalent in 6.1% and 5.1% patients, respectively[428,429]. Moreover, the socioeconomic burden of DR-induced visual impairment or blindness, particularly in the working age group, is a serious concern[430]. Therefore, it is high time to devise the means of managing DR and bring the problem under control[431]. A systematic approach to health education, creating awareness among patients and various health personnel, and matching it with appropriate screening and service delivery mechanisms will go a long way. Early detection and management of DR with quick referrals and highly coordinated teamwork between the endocrinologists, ophthalmologists, neurologists, and nephrologists could reduce the prevalence of DR in India[432]. Necessary therapeutic measures in managing DR include optimum glycemic levels, lipid and hypertension control. In severe cases of pre-proliferative DR, laser pan-retinal photocoagulation (PRP) is indicated to prevent the progression of DR and vision loss[433]. Of note, Implementation of intensive glycemic control can cause transient (early) worsening, primarily due to the development of small arteriolar infarcts, which result in the well-known cotton wool spots, particularly in patients with poor control and long-standing disease are at risk. Therefore, a calculated and stepped approach should be adapted to manage hyperglycemia in patients with DR[434].

Rationale and Evidence

Screening

- Several guidelines emphasize on eye screening in T2DM, however, it appears they are divided on the frequency of screening. Some recommend annual screening (NICE- UK) while others recommend screening every 1–2 years (Canadian-Canada, Australian-Australia and SIGN-Scotland).
- With regard to frequency of screening in limited care setting, the panel endorsed the ADA recommendation which suggests less-frequent examinations (every 2–3 years) following one or more normal eye examinations[435].
- Screening methods for DR include direct and indirect ophthalmoscopy, slit-lamp bio-microscopy, stereoscopic color film fundus photography, mydriatic or nonmydriatic digital color, and monochromatic photography[436–438].
- In-person clinical exam by an eye care provider is the gold standard for diagnosing DR, faster digital retinal imaging acquisition and grading of DR using fundus images obtained with a nonmydriatic fundus camera is now being considered a practical, cost-sparing, and feasible screening tool for the early detection of DR, and preventing blindness[439].

Counselling pregnant women

- DR is the foremost cause of blindness in women during antenatal period, and pregnancy increases the short-term risk of DR progression[437]. The possible relationship between DR and the perinatal outcome has been addressed in several studies[440,441]. Women with more severe DR were more likely to develop obstetric complications20,21,, and those with proliferative changes accounted for a higher incidence of congenital malformations and/or fetal death[441].
- As pregnancy can induce progression of DR, the panel recommended pre-conception counselling for women, clearly explaining the risk of progression of DR during pregnancy, especially if they already have proliferative retinopathy. They should be advised on maintaining reasonable glycaemic control before and throughout pregnancy under the guidance of a healthcare professional. In addition, the panel emphasized the need for close follow-up during pregnancy and up to 1 year post-partum and monitoring for progression of DR and co-existing hypertension and renal disease, if any.

Guarded prognosis after intra-ocular lens surgery

- Though surgical interventions are crucial for cataract management, in most of the patients, particularly those with complicated cataracts,

vision may not be restored. These patients eventually develop corneal decompensation, glaucoma, and optic atrophy[443]. Because the prognosis of the retina is poor, especially in the presence of mature cataract, the panel suggested that it is crucial to educate the patient about the guarded prognosis for regaining vision after IOL surgery.

Evidence

Though evidence from past studies suggests that the prevalence of DR is low in Indians compared to other ethnic groups, emerging data indicate significant increase in prevalence of retinopathy in South Asians compared to Caucasians[444]. Data from a population- based study (CURES) indicate that the overall prevalence of DR in urban south Indian population was 17.6%, with higher prevalence among men than in women (21.3% vs. 14.6%; p<0.0001) and among subjects with proteinuria (p=0.002)[445]. Similarly, prevalence of DR in western India was found to be 33.9%[446]. Data from a recent population-based cross-sectional study suggests that one of 10 individuals in rural South India, above the age of 40 years, had evidence of DR[447]. A meta-analysis of seven studies from India found 14.9% of known diabetes patients aged ≥30 years and 18.1% among those aged ≥50 years had DR. Furthermore, no linear trend was observed between age and the proportion with DR[448]. Duration of diabetes, HbA1c, male gender, macro-albuminuria, and insulin therapy were strongly associated with increased risk of DR among South Indians[449,450]. Moreover, the risk of nephropathy (OR: 5.3, p<0.0001) and neuropathy (OR: 2.9, p<0.0001) was significantly higher among T2DM patients with DR compared to those without DR[451,452]. After adjusting for age, gender, HbA1c, SBP, serum triglycerides, and duration of diabetes, DR was significantly associated with nephropathy (p=0.005) than with neuropathy[451]. Another study showed HbA1c, BMI, duration of diabetes, microalbuminuria and peripheral neuropathy are contributing factors in the degree of retinopathy (p=0.001). This correlation was explained by common mechanisms involved in tissue damage by all these factors. Microalbuminuria was positively correlated with retinopathy in T2DM patients and may be a marker for the risk of severe and proliferative retinopathy development. Microalbuminuria was associated cross-sectionally with the presence of retinopathy in patients with T2DM. This study suggests that microalbuminuria may be a marker for the risk of proliferative retinopathy development[453]. Recent studies have also started shedding light on the association of dyslipidemia with DR. [454]

Implementations

A sufficient number of trained general ophthalmologists and general physicians are required to develop an integrated DR model that facilitates early detection and create awareness of DR. Medical camps should be conducted for screening of diabetes and retinopathy, which will help to identify people at risk of sight-threatening DR and initiate treatment including laser photocoagulation or vitreous surgery. Mobile vans with a fundus camera or other low-cost tools that can be used in remote rural areas should also be explored. However, successful program implementation requires a team approach involving both administrative and voluntary organizations.

Telemedicine-based DR screening costs less ($10 vs $25) than conventional retinal examination and the telemedicine-based digital retinal imaging examination has the potential to provide an alternative method with greater convenience and access for remote and indigent populations. This cost-effective technology-driven model would prevent the screening costs, help in the early detection of DR, and prevent a common cause of blindness. Telemedicine should be encouraged to improve access and increase compliance with annual evaluation, at a low cost for patients with diabetes.[455] Tele-diabetes shares some of the same attributes as telemonitoring for other chronic conditions, such as congestive heart failure, stroke, and chronic obstructive pulmonary disease. In a pilot study conducted in Hungary on patients with diabetes, 30% of the patients had never participated in any ophthalmological screening. In comparison, 25.7% had DR of some grade based upon a standard fundus camera examination and the UK- based DR grading protocol (Spectra™ software). Majority of the patients were satisfied with the screening and found it reliable and acceptable to undertake examination under pupil dilation; 67.3% were willing to undergo nonmydriatic fundus camera examination again. Participants found digital retinal screening to be reliable and satisfactory. Telemedicine can be a vital tool, supporting eye care professionals and allowing for faster and more comfortable DR screening[456].

NEUROPATHY

Recommendations

Recommended Care

- All patients with T2DM should be assessed for diabetic neuropathy at the time of initial diagnosis and annually.
- Diagnose sensorimotor nerve damage by history and examination (10 g monofilament with or without temperature, non-traumatic pin-prick, vibration [128 Hz tuning fork], ankle reflexes), and/or simple quantitative testing (e. g. biothesiometer vibration perception). Use serum B12, thyroid function tests, creatinine/urea, alcohol abuse, and medication history to exclude other causes.
- Diabetic Neuropathy Symptom Score (NSS) and Neuropathy Disability Score (NDS) in T2DM population has been found to be a useful resource in evaluating diabetic sensorimotor polyneuropathy as an important bed side tool.
- Diagnose symptomatic (painful) diabetic neuropathy by excluding other possible causes of the symptoms. Manage by stabilizing blood glucose control, and treatment with tricyclic antidepressants if simple analgesia is not successful. If a one-month trial of tricyclic therapy is not successful, further treatment options include pregabalin/gabapentin and duloxetine, then tramadol and oxycodone.
- Weight gain and lifestyle measures need reinforcement with the use of antidepressants and gabapentin, and pregabalin.
- Further management requires typically referral to a pain control team. Be aware of the psychological impact of continuing symptoms, particularly if sleep is disturbed. In patients with diabetic neuropathy and co-morbid depression, anxiety, and sleep loss, duloxetine should be preferred.
- A visual record of a simple graphic tool to measure response to therapy must be mandated, which will save patients from over/unnecessary treatment.
- Tools, e. g., pain scale should be encouraged in clinical practice.
- Diagnose erectile dysfunction by history (including medication history), exclusion of endocrine conditions (measure prolactin and testosterone), and a trial of a phosphodiesterase type-5 (PDE5) inhibitor (where not contraindicated by nitrate therapy). Consider other approaches such as intra-urethral or intracavernosal drugs and sexual & relationship counselling, where PDE5 inhibitors fail or cannot be used.
- Discourage the use of alternative medicines as they can cause further complications.
- Diagnose gastroparesis by history, trial of a prokinetic drug (metoclopramide, domperidone), and if troublesome, by gastric emptying studies.
- Diagnose CV autonomic neuropathy by resting heart rate and heart rate response to provocation tests (lying-standing, Valsalva, deep breathing), and by lying and standing BP. Inform anaesthetists, when relevant, where this is present.
- Every patient must undergo a simple assessment e. g. questionnaire-based assessment for depression.

Limited Care

- Screen and diagnose sensorimotor nerve damage by history of symptoms, and sensory assessment by 10g monofilament or tuning fork with/without non-traumatic disposable pin-prick.
- NSS and NDS in T2DM population has been found to be a useful resource in evaluating diabetic sensorimotor polyneuropathy as an important bedside tool.
- Manage symptomatic (painful) diabetic neuropathy by excluding other causes, stabilizing glycemic control, and treatment with tricyclic antidepressants if simple analgesia is unsuccessful. Opiate analgesia may be necessary as locally available.
- Assess erectile dysfunction by history and examination and consider possible contributions of other medication or disease.

Background

Neuropathy is among the most common life-threatening complication of diabetes that involves both peripheral and autonomic nerves, affecting up to half of all diabetic patients. Hyperglycemia-induced polyol pathway, injury from AGEs, and enhanced oxidative stress have been implicated in its pathogenesis[457,458]Peripheral neuropathy in diabetes appears in several forms depending on the site, manifesting as sensory, focal/multifocal, and autonomic neuropathies.[459] Diabetic neuropathy has resulted in more than 80% of amputations after foot ulceration or injury. It is among the most common, expensive, and disabling complications of diabetes, affecting approximately 30% of hospitalized patients with diabetes and 25% of patients with diabetes in the community[460]. About 30% of patients with known or newly diagnosed diabetes suffer from diabetic neuropathy[461,462]. In the cross-sectional survey of Indian patients with T2DM in CINDI and CINDI2 studies, diabetic neuropathy was prevalent in 13.15% and 13.2% of patients, respectively[463,464]. As per the Toronto Consensus Panel, diabetic polyneuropathy is a "symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and micro-vessel alterations as a result of chronic hyperglycemia exposure and cardiovascular risk covariates"[465]. The most common form of diabetic neuropathy is the distal symmetrical polyneuropathy that involves both tibial and sural nerves[466]. The presence of neuropathy is associated with significant morbidity, including recurrent foot infection and ulcers, impotence in men with diabetes, and sudden death in individuals with CV autonomic neuropathy.[467–470] Neuropathic pain in patients with diabetes is commonly encountered in clinical practice[466,471]. The present recommendations provide insights into the management aspects of diabetic neuropathy while exploring newer therapeutic options that have emerged in recent years.

Rationale and Evidence

Detection of sensorimotor polyneuropathy

- Though nerve conduction studies are powerful tools for identifying cases of diabetic neuropathy[472], NSS[473] and NDS[474] in T2DM patients were found to be a valuable resource for evaluating diabetic sensorimotor polyneuropathy as a bedside tool[475]. A cross-sectional study in T2DM patients that examined the nerve conduction velocities of motor and sensory nerves, using NSS and NDS in patients with clinically detectable neuropathy showed significant electrophysiological changes with the duration of T2DM[475]. Similar results were observed in another study where NSS and NDS helped in prompt evaluation of diabetic sensorimotor polyneuropathy and in diagnosing subclinical cases[476–478]. A study that validated the use of NSS and NDS for clinical diagnosis of peripheral neuropathy in middle aged 855 T2DM patients showed that NSS and NDS can detect diabetic neuropathy with a sensitivity of 71.1% and specificity of 90% and was found to be simple, acceptable, reproducible and validated method for early diagnosis of diabetic neuropathy[479,480].
- The panel emphasized on neurological examination using NSS and NDS as it is important bed-side tool and a useful resource in evaluating diabetic sensorimotor polyneuropathy.
- Type 2 diabetes patients with abnormal ABI were predicted to have a 27% increased odds ratio of CAD outcome and 80% in the presence of nephropathy. Thus, as part of comprehensive diabetes care, albuminuria screening and ABI measurement are suggested.[481]
- Recent studies have also shed light on the severe microvascular complications and surrogate markers to detect the same.[482–484]

Management of diabetic neuropathy [Figure]

Diabetic peripheral neuropathic pain can be managed with several classes of drugs including tricyclic antidepressants, anticonvulsants, serotonin-norepinephrine reuptake inhibitors, opiates and opiate-like substances, and topical medications.

- Tricyclic antidepressants are recommended as first-line therapy for diabetic peripheral neuropathic pain in appropriate patients.
- Gabapentin is an anticonvulsant structurally related to γ-aminobutyric acid (GABA), a neurotransmitter that plays a role in pain transmission and modulation. In patients with a history of pain attributed to diabetic neuropathy, gabapentin monotherapy was efficacious for treating pain and sleep interference associated with diabetic peripheral neuropathy along with positive effects on mood and quality of life[485].
- Duloxetine and pregabalin were approved by the USFDA in 2004 and tapentadol extended release were approved in 2012 for the treatment of painful diabetic neuropathy (PDN)[486].
- Pregabalin is a potent gabapentinoid used in the management of PDN. Several double-blind placebo-controlled trials have reported the dose dependent (600 mg/daily) efficacy of pregabalin; however, several side effects, including mood disturbance, ankle oedema and sedation also have been reported[487–489].
- Both duloxetine and pregabalin are effective; however, a significant improvement in QoL of patients was obtained by duloxetine with comparatively mild increase in the price[490].
- Duloxetine is a selective inhibitor of the reuptake of both 5-hydroxytryptamine and norepinephrine[491,492]. Results from randomized-controlled clinical trials reveal that duloxetine provides significantly more diabetic neuropathic pain relief than either placebo or routine care, with higher safety and tolerability[493–495]. Moreover, a recent Cochrane collaboration review including data from eight studies and 2728 participants reported that 60 mg and 120 mg daily doses of duloxetine were efficacious. Still, lower doses were not associated with improvement in the PDN management[496].
- Tapentadol, an opioid analgesic, may act via opioid spinal-supraspinal synergy, as well as intrinsic spinally mediated μ-opioid receptor agonist-norepinephrine reuptake inhibitor effect[497]. The efficacy and safety of tapentadol were also published in several clinical trials[498,499]. Tramadol may also be used for pain management. However, there is only modest information about the use of tramadol in neuropathic pain, primarily from small, largely inadequate studies[500]. Further, a fixed-dose combination of tramadol/paracetamol might be a useful pharmacological option for chronic pain management, particularly in elderly patients[501].
- Neuropathic pain can be severe, impact quality of life, limit mobility, and contribute to depression and social dysfunction[502]. Management of underlying depression is a must to improve QoL. Tricyclic antidepressants, venlafaxine, carbamazepine, and topical capsaicin, although not approved for the treatment of painful diabetic neuropathy, may be effective and considered for the treatment[503–506].
- Capsaicin has been used with some success in the treatment of patients with PDN. It binds to the receptor that opens the TRPV1 causing sodium and calcium influx and substance P release occurs, Repeated TRPV1 exposure to capsaicin causes substance P depletion and TRPV1 desensitization and defunctionalization[507].
- Lidocaine blocks the voltage-gated sodium channels and stabilizes the neuronal membrane potential, reducing ectopic discharges and raising peripheral ectopic discharge threshold, causing reduced pain transduction[508].

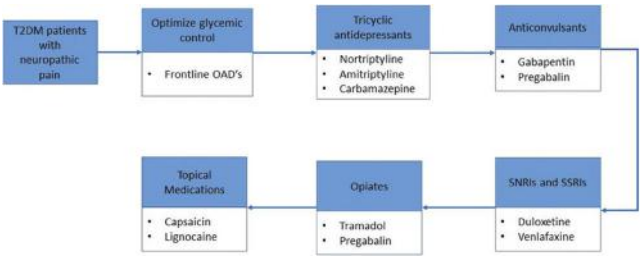


Figure 7: Management algorithm for neuropathy. OADs: Oral antidiabetics; SNRIs: Serotonin-norepinephrine reuptake inhibitors; SSRIs: Selective serotonin reuptake inhibitors

Implementation

Appropriate protocols should be developed for sensory testing and may include formal assessment using the NSS and NDS. Recommended medications should be available according to the level of resources. Medical

teams need to remain trained in the diverse manifestations of autonomic neuropathy[467].

DIABETIC KIDNEY DISEASE

Recommendations

Recommended Care

- Kidney function should be assessed at diagnosis and annually by:
  - Urine test for albuminuria
  - Measurement of serum creatinine and calculation of eGFR
- Urinary albumin to creatinine ratio (ACR) measurement in an early morning first void (mid-stream) spot specimen is the preferred method for assessment of microalbuminuria/proteinuria. Where a first void specimen is not possible or practical, a random spot urine specimen is acceptable. ACR can be measured in the laboratory or at site-of-care.
- Control hyperglycemia, exclude urinary or systemic infections, or pyrexia and avoid strenuous exercise before testing for albuminuria.
  - If ACR is raised (microalbuminuria) i.e. ACR >30 mg/g creatinine, repeat ACR twice over the following four months:
    - » Microalbuminuria is confirmed if ACR is elevated in two out of three tests, in the absence of infection or overt proteinuria
    - » If both repeat tests are not raised, check again annually
    - » An ACR >300 mg/g indicates macroalbuminuria
- DKD is diagnosed on the basis of a raised urine albumin/protein or a reduced eGFR (<60 mL/min/1.73 m^2) calculated from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. CKD-EPI is the preferred formula.
- The Modification of Diet in Renal Disease (MDRD) formula for calculation of eGFR is not validated above 70 years of age and in Indian patients.
- For patients <18 years of age (including infants, toddlers, children, and teens), the Bedside Schwartz equation should be used.
- Individuals with DKD should be managed as follows:
  - Identified high-risk individuals (hypertensives, duration of diabetes >3-5 years, family history of nephropathy/HF/ASCVD) must get preference for SGLT2 inhibitors for glycemic management if feasible and accepted by patients (eGFR >30 mL/min/1.73 m^2)
  - Use angiotensin converting enzyme (ACE)-inhibitors or angiotensin receptor blockers (ARBs) in individuals with micro-or macro-albuminuria, titrated to the maximum tolerated dose
  - Intensify management of BP (target ≤130/80 mm Hg) using BP lowering medications and dietary modification (low salt and reduced protein intake)
  - Intensify management of blood glucose
  - Monitor ACR, eGFR and serum potassium
  - Advise daily limiting protein intake to 1 g/kg of high biological value protein. In those with advancing CKD, restrict to 0.8 g/kg daily with advice for caution in patients consuming a non-vegetarian diet
- Intensify other renal and CV protection measures
- Assessment and management of anemia and bone disease and appropriate vaccination
- Smoking leads to progression to end-stage renal disease (ESRD) in diabetes, so patients must be counselled to quit smoking
- Consider referral to nephrologists when there is uncertainty about the etiology of kidney disease, complex management issues (stress, obesity, high uric acid, UTIs, anemia for timely use of Erythropoietin analogues, BP to targets, Nocturnal BP control stressed)
- Agree to a referral criterion for specialist renal care between local diabetes specialists and nephrologists. Referral criteria might include
  - eGFR<30 mL/min/1.73 m^2, progressive deterioration of kidney function, persistent proteinuria, biochemical or fluid retention problems or difficult diagnosis (to rule out non-diabetic renal disease where fundus is normal and no proteinuria).
- Rule out non-diabetic kidney disease in patients with early onset of nephropathy (<5 years), absence of retinopathy, heavy proteinuria, presence of active urinary sediments or unexplained rapid decline in eGFR.

Limited Care

- Check annually for proteinuria in an early morning urine sample (or a random sample) using a dipstick. If the test is positive exclude UTIs by microscopy (and culture if possible).
- Measure serum creatinine and calculate eGFR annually.
- A simple, inexpensive screening procedure for urinary protein excretion which can be used as a diagnostic test in outpatient has been reported in the Indian population. Estimated proteinuria is useful in the serial evaluation of kidney function.
- Manage those with proteinuria as follows:
  - Consider use of ACE inhibitors or ARBs and SGLT2 inhibitors unless contraindicated or issues with tolerability
  - Aim for BP ≤130/80 mm Hg using any BP lowering medication and control of salt intake [Table]
  - Aim to achieve targets for blood glucose control
  - Aim to improve lipid profile using available medications
  - Check proteinuria status annually
  - Measure serum creatinine and calculate eGFR annually

Background

Previously known as diabetic nephropathy, DKD is defined as diabetes with albuminuria (ratio of urine albumin-to- creatinine ≥30 mg/g), impaired glomerular filtration rate (<60 mL/min/1.73 m^2), or both and is now recognized as the strongest predictor of mortality in patients with diabetes[509]. It is a leading cause of ESRD affecting ~20–30% diabetes patients, and is associated with increased CV mortality[510]. It affects 10–40% of T2DM patients who eventually suffer from kidney failure[511,512]. In the cross-sectional survey of Indian patients with T2DM in CINDI and CINDI2 studies diabetic nephropathy was prevalent in 1.06% and 0.9% of patients respectively[513,514]. The cost of treatment for advanced DKD is substantial. Less than 10% of ESRD patients have access to any kind of renal replacement therapy[515,516]. Thus, in a country with limited resources, it becomes appropriate to direct efforts toward the prevention of DKD rather than the treatment.

Pathophysiology of diabetic kidney disease

The pathophysiological mechanisms of DKD are complex and are often evident by intrarenal hypertension, compromised GFR and microalbuminuria. Microalbuminuria, is the first and most critical manifestation of diabetic nephropathy, which when progressed to overt albuminuria (increased albumin levels in the urine) indicates severe renal dysfunction culminating to renal failure[517]. The presence of microalbuminuria is a powerful marker of cardiovascular disease and all-cause mortality[518]. Thus, the presence of diabetes, particularly accompanied by microalbuminuria, is most often considered a warning signal for CV risks in patients with diabetes.

DKD is characterized by a constellation of histopathological changes beginning from glomerular hyperfiltration causing glomerular basement membrane thickening, progressive accumulation of extracellular matrix in glomerular mesangium and tubulointerstitium, causing mesangial expansion and Kimmelstiel–Wilson nodules (an aggregation of mesangial cells and mesangial matrix), arterial hyalinosis, and tubulointerstitial changes [Figure 9]. Additionally, podocyte dropout is also a critical factor for DKD development. Podocytes are known to distort and change their size and shape to accommodate or cover the openings created by the basement membrane thickening causing them to shift or dropout.

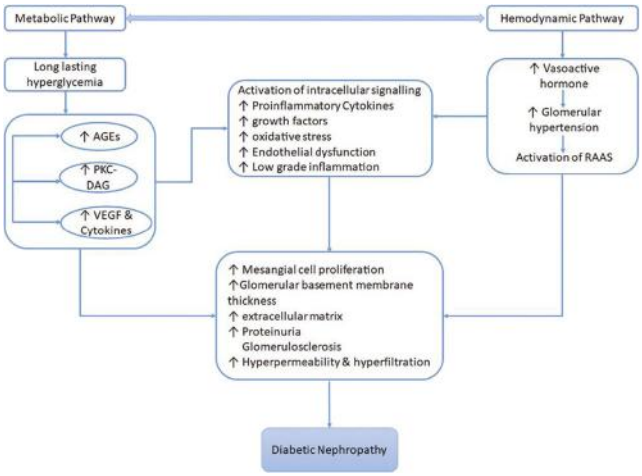


Figure 8: Pathophysiology pathways in diabetic kidney disease. AGEs: Advanced glycation end products; PKC-DAG: Protein kinase C-diacylglycerol;RAAS: Renin-angiotensin-aldosterone-system; VEGF: Vascular endothelial growth factor

In India, with an increase in the prevalence of diabetes, it becomes imperative to evolve definite guidelines for the detection of diabetic nephropathy and suggest practical clinical recommendations to combat it. Improving glycemic control, aggressive antihypertensive treatment, and the use of ACE inhibitors or ARBs will slow down the rate of progression of nephropathy[519,520]. In addition, protein restriction and other treatment modalities such as phosphate lowering may have benefits in selected patients[521]. Careful consideration should be given to normoalbuminuric kidney disease in patients with T2DM. Although the serum creatinine is usually normal, most normoalbuminuric patients with DKD have an eGFR <60 mL/min/1.73 m^2 per the MDRD formula. However, as expected, because of normoalbuminuria and other favorable characteristics, their risk for DKD progression or death is lower.[522]

Rationale and Evidence

Identification and monitoring and diabetic kidney disease: Persistent microalbuminuria is the earliest sign of diabetic nephropathy or DKD. The diagnostic reference standard for defining microalbuminuria is the detection of 30 to 300 mg of albumin in a 24-h urine sample and is the first-line annual screening test for most persons with diabetes. It is recommended that once a screening test detects microalbuminuria, it should be confirmed with additional spot urine tests over the next three to six months. The Kidney Disease Outcomes Quality Initiative (KDOQI)-Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease by the National Kidney Foundation (NKF), recommend that patients with diabetes should be screened annually for CKD: 5 years after the diagnosis of type 1 diabetes and from onset/diagnosis of type 2 diabetes. The presence of albuminuria must be evaluated based on the UAE concentration or Urinary albumin-to-creatinine ratio (UACR) in untimed (spot) urine specimens and by estimating the glomerular filtration rate from serum creatinine measurements by using prediction equations[523,524]. The ADA recommends identifying and monitoring DKD based upon assessments of kidney function with an estimated GFR (eGFR), 60 L/min/1.73m^2, or kidney damage by estimation of albuminuria 30 mg/g creatinine along with annual screening for microalbuminuria. Clinical recommendations by the ADA for DKD screening also suggest that persons with type 1 or 2 diabetes and microalbuminuria should continue to be tested for albuminuria annually to monitor disease progression and response to therapy[525].

- Estimated Protein Excretion (EPE) is a method of estimating ACR in a random urine sample to assess renal function in patients with diabetes. EPE was found to be useful in the serial evaluation of kidney function in Indian patients with diabetes[526,527]. Moreover, EPE is a simple and inexpensive screening procedure for urinary protein excretion, which can be used as a diagnostic test in outpatient wards, particularly in developing countries like India.
- As EPE is an inexpensive screening procedure to assess kidney function, the panel recommended it for use in the Indian population who are at risk of diabetic nephropathy.
- Screening of microalbuminuria and estimating glycated albumin can help in the clinical management of diabetic nephropathy[528]. Screening for albuminuria by measuring urine albumin concentration or estimating ACR is acceptable in the Asian population[529]. However, evidence suggests that vigorous exercise even for short periods (15–20 min) leads to ACR above the microalbuminuria threshold even in healthy participants[530,531].
- Based on evidence, the panel suggested that physicians should ask about recent vigorous exercise and avoid measuring urine albumin excretion for at least 24 h in the presence of same.
- Microalbuminuria shows a strong association with increased CVD risk in diabetic patients in Indian population[532–534].
- A recent cross-sectional study in diabetic nephropathy patients showed a positive correlation between eGFR and cortical renal thickness. Cortical renal thickness was a better predictor of renal function than bipolar renal length.[535]

Management of hyperglycemia in patients with diabetic kidney disease

In patients with DKD, when selecting and dosing glucose-lowering drugs, renal function has to be assessed and periodically monitored during treatment to detect changes that may affect drug metabolism and excretion. While mild renal insufficiency can be treated with most OADs, patients with DKD stage 3-5, most often require treatment adjustments according to the degree of renal insufficiency.

Combinations of therapies are available for the management of hyperglycemia in patients with type 2 diabetes. Metformin is a first-line agent in all patients, including patients with DKD. Second-generation sulphonylureas are also commonly used. Although, the reduction in HbA1c is modest with an average between 0.5-1.0%, DPP-4 inhibitors can be safely used at the appropriate dose in DKD. SGLT2 inhibitors and DPP-4 inhibitors are responsible choices in moderate to severe cases of DKD [Table 14].

Oral antidiabetics that exert renoprotection

- Evidence suggests that two oral hyperglycemic agents DPP-4 inhibitors[536] and SGLT2 inhibitors, exert renoprotective effects in patients with diabetes. SGLT2 inhibitors are indicated to improve glycemic control in adults with T2DM by reducing the reabsorption of filtered glucose. They can also lower the renal threshold for glucose, thereby increasing urinary glucose excretion.
- While these medications have been used safely in patients with Stage 3 DKD (eGFR down <30 mL/min), the glycemic reduction response to the SGLT2 inhibitors declines with decreasing kidney function, as a decrease in eGFR results in a decrease in urinary glucose excretion.
- Canagliflozin has been approved for use in patients with eGFR>45 mL/min/1.73 m^2, with a dose limited to 100 mg once daily in patients with eGFR 45≤60 mL/min/1.73m^2. Empagliflozin can also be used in patients with an eGFR down to 45 mL/min/1.73 m^2, while dapagliflozin is approved in patients with an eGFR down ≥60 mL/min/1.73 m^2. Regular assessment of renal function is recommended with the use of any of these SGLT2 inhibitors.
- Recently completed CREDENCE study reported that at a median follow-up of 2.62 years, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group[537]. In the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program, canagliflozin treatment was associated with a reduced risk of sustained loss of kidney function, attenuated eGFR decline, and a reduction in albuminuria. These encouraging results

suggest that canagliflozin exerts renoprotective effect in patients with T2DM[538].

- The EMPA-REG OUTCOME trial evaluated the non-inferior cardiovascular safety of empagliflozin in high- CV-risk T2D patients with an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73 m^2. Empagliflozin reduced the rate of new onset or worsening nephropathy, which were defined as new-onset microalbuminuria, doubling of creatinine, and eGFR ≤ 45 mL/min/1.73 m^2, initiation of renal replacement therapy, and death due to renal disease (hazard ratio [HR]: 0.61, 95% confidence interval [CI]: 0.53–0.70; p < 0.0001)[539].
- Results of the DECLARE–TIMI 58 cardiovascular outcomes trial suggest that, in patients with T2DM, Dapagliflozin prevented and reduce the progression of renal disease[540].
- The DAPA-CKD trial concluded that among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo. [541]
- The EMPA-Kidney study in an ongoing randomised controlled trial. The primary aim of the study is to investigate the effect of empagliflozin on kidney disease progression or cardiovascular death versus placebo on top of standard of care in patients with pre-existing chronic kidney disease. [542]

Protein restriction

- IDF recommends limiting protein intake to 1 g/kg body weight daily among individuals with DKD, if they are found proteinuric. Similarly, ADA recommends protein intake should be 0.8 g/kg/body weight/day in patients with DKD[543]. In the Indian context, the source of protein is mainly from vegetable and animal oils and daily protein consumption is about 0.6–0.8 g/kg body weight.[544] Furthermore, protein content in non-vegetarian diet was found to be higher when compared to the vegetarian diet.[545] In addition, evidence suggests that animal protein may aggravate the risk of diabetes[546]. Therefore the panel emphasized on protein restriction and avoiding extra protein intake, particularly in non-vegetarians with nephropathy.

Smoking

- Smoking is associated with hyperglycemia, dyslipidemia and decline in GFR which leads to the progression of ESRD in patients with diabetes[547,548]. Smoking tends to induce albuminuria and abnormal renal function through formation of advanced glycated end products (AGEs), which are responsible for advanced vascular permeability and kidney damage.[549] A recent systematic review reported that consumption of ≥15 packs of cigarettes/year increases the risk of progression of DKD[550]. Moreover, data from a recent study in India suggests that compared to non-smokers the prevalence of microalbuminuria in smokers was 4-fold higher[551].
- The panel opined that patients must be counselled against tobacco use and encouraged to quit smoking to reduce the risk of progression to ESRD.

Referral to specialist

The panel endorsed IDF recommendation on referral criteria; however, it was suggested that, most of the patients at this stage of diabetic nephropathy require a specialist care which may not be available at primary care or single physician center. Hence, local diabetes specialists should refer the patient to specialist renal care center/nephrologist. Likewise, nephrologists should refer patients to specialist renal care if the patient presents with following condition:

- eGFR<30 mL/min/1.73 m^2
- progressive deterioration of kidney function
- persistent proteinuria, biochemical or fluid retention problems or
- difficulty in diagnosis (to rule out non diabetic renal disease where fundus is normal and proteinuria is not present).

Table 15: Stratifying target blood pressure as per clinical condition

Guideline	Recommendation
ADA 2019[451]	<140/90 mmHg is recommended to decrease CVD mortality and slow down CKD progression Lesser targets such as <130/80 mmHg might be considered in individuals with albuminuria and at increased risk of CVD and CKD progression While achieving <130 mmHg SBP target, especially in old people, care should be taken to avoid DBP levels <60-70 mmHg
KDIGO 2012[452]	In DKD patients, not requiring dialysis, with UAE <30 mg/day and office BP consistently below 140/90 mm Hg, a target of ≤140/90 mmHg is recommended In DKD patients, not requiring dialysis, with UAE >30 mg/day and office BP consistently >130/80 mm Hg, a target of ≤130/80 mmHg is recommended

ADA: American Diabetes Association, BP: Blood pressure, CKD: Chronic kidney disease, CV: Cardiovascular, CVD: CV disease, DKD: Diabetic kidney disease, SBP: Systolic BP, DBP: Diastolic BP, UAE: Urinary albumin excretion

Indian evidence

- Prevalence of microalbuminuria is strongly associated with age, DBP, HbA1c, FPG and duration of diabetes[552,553].
- A positive co-relation between urine albumin excretion rate and eGFR <60 mL/min/1.73m^2 was observed indicating that these two parameters provide a complimentary benefit in management of CKD[554].
- Vitamin D deficiency can have significant impact on albuminuria. Therefore supplementation with calcitriol should be considered in these patients as it has been shown to provide beneficial effects on microalbuminuria[555].

Implementation

Management of DKD requires access to healthcare professionals, laboratory for ACR and creatinine estimations, and the availability of multiple blood-pressure-lowering medications, in particular renin-angiotensin system blockers.

Table 16: Dose adjustment for oral antidiabetics agents for patients with diabetic kidney disease

Class	Dose adjustments
Metformin	Metformin can be used till to GFR 30 GFR ≥45-59: use caution with dose and follow renal function GFR ≥30-44: max dose 1000 mg/day or use 50% dose reduction. Follow renal function every three months GFR: <30: avoid use
Second-generation SU	Glipizide: GFR <30: Use with caution Glimepiride: GFR <60: Use with caution; <30: Avoid use Glyburide: Avoid use Gliclazide-upto GFR 30: No dose adjustment; <30: Low dose preferred
TZD	No dose adjustment
Alpha-glucosidase Inhibitors	Acarbose: Serum creatinine >2 mg/dL: Avoid use Miglitol: GFR <25 or serum creatinine >2 mg/dL: Avoid use
DPP-4 inhibitor	Sitagliptin: GFR≥50: 100 mg daily; GFR 30-49: 50 mg daily GFR <30: 25 mg daily Saxagliptin: GFR >50: 2.5 or 5 mg daily; GFR ≤50: 2.5 mg daily Linagliptin: No dose adjustment Alogliptin: GFR >60: 25 mg daily; GFR 30-59: 12.5 mg daily; GFR <30: 6.25 mg daily Tenaligliptin 20 mg/day - No dose adjustment
SGLT2i	Canagliflozin: GFR 45-<60: Maximum dose 100 mg OD; GFR<45: avoid use Dapagliflozin[541]: GFR <60: Avoid use Empagliflozin[542]: GFR <45: Avoid use
Mineralocorticoid Receptor Antagonists (MRA)	MRA- Finerenone[556] : full dose : 20-mg daily. eGFR: 25–60 ml/min per 1.73 m2 or serum potassium 4.8–5 mEq/L,10 mg daily

GFR: Glomerular filteration rate, SU: Sulfonylureas, OD: Once daily, TZD: Thiazolidinedione, DPP-4: Dipeptidyl peptidase, SGLT2i: Sodium-glucose co-transporter 2 inhibitors

CHRONIC COMPLICATIONS 2: DIABETIC FOOT AND PERIPHERAL ARTERIAL DISEASE

Recommendations

Recommended Care

- Assess feet of patients with diabetes at every visit for lesions requiring active treatment and for risk factors for ulcer and amputation:
  - History of previous foot ulceration or amputation, symptoms of peripheral arterial disease (PAD), physical or visual difficulty in self-foot-care
  - Foot deformity (hammer or clawed toes, bone prominences), visual evidence of neuropathy (dry skin, dilated veins) or incipient ischemia, callus, nail deformity, or damage. Patient footwear should also be assessed
  - Detection of neuropathy by 10 g Semmes Weinstein monofilament (or 128 Hz tuning fork); a biothesiometer (to assess vibration perception threshold) is an option for quantitative assessment (cut-off point for ulcer risk >25 volts) and non-traumatic pin-prick.
  - Michigan Neuropathy screening instrument is a useful, easy-to-use epidemiological tool to assess neuropathy in a patient with diabetes.
  - Palpation of foot pulses (dorsalis pedis and posterior tibial). Doppler ultrasound examination or ankle: brachial pressure (ABI) ratio (<0.9 for occlusive vascular disease) may be used where pulses are diminished to quantify the abnormality.
- Discuss the reasons for foot review with each patient with diabetes, as part of the foot-care educational process.
- Must completely refrain from walking barefoot, including visiting religious places.
- Timely screening and early detection of diabetic neuropathy may help prevent the progression to diabetic foot.
- Agree upon a foot-care plan based on the findings of an annual foot review with each person with diabetes. Assess and provide necessary foot-care education according to individual needs and risks of ulcer and amputation.
- F18PET/CT (labeled WBC) may be considered (if available) to confirm osteomyelitis in the complicated diabetic foot; if MRI is contraindicated because of CKD.
- Classify and manage according to risk classification level based on findings of foot assessment.
- People with foot ulceration or infection require the following management:
  - Pressure offloading
  - Refer to a multidisciplinary foot-care team within 24 h for:
    - » Appropriate wound management, dressings, and debridement as indicated
    - » Infections should be classified as mild (superficial with minimal cellulitis), moderate (deeper than skin or more extensive cellulitis), or severe (accompanied by systemic signs of sepsis). Consideration of systemic antibiotic therapy (often longer term) for extensive cellulitis or bone infection as

indicated.
  - First-line medications: generic penicillin, cephalosporins, macrolides, clindamycin and/or metronidazole, as indicated
  - Second-line medications: amino-quinolones co-amoxicillin, imipenem.
  - Medical treatment may be considered as an adjunct after TCC.
  - Methylprednisolone and bisphosphonates have not been shown to reduce the time to remission.
  - Rivoraxaban for PAD also has promising outcomes in diabetic foot patients
- » Probing to bone, radiology and scans, magnetic resonance imaging and biopsy were indicated for suspected osteomyelitis
- » Reduce weight bearing, relief of pressure (walking with crutches, rest) offloading and optimal pressure distribution (casting, if indicated)
- » Investigation and treatment (referral) for vascular insufficiency
- » Specialist therapeutic footwear and orthotic care (e. g. insoles) and individualized discussion of prevention of recurrence, when an ulcer has healed
- » Optimal blood glucose control

- Patients with foot complications, including DFU have an increased risk of mortality and need close monitoring for cardiovascular events.
- Tc 99m uptake scan may be considered for the diagnosis of Charcot, if MRI is contraindicated.
- Amputation should not be considered unless:
  - A detailed vascular evaluation has been performed by the vascular team
  - Ischemic rest pain cannot be managed by analgesia or revascularization
  - A life-threatening foot infection cannot be treated by other measures
  - A non-healing ulcer is accompanied by a higher burden of disease that would result in amputation.
  - Management of Charcot's foot will include
    - *Non-surgical treatment:* offloading (casting), walking in a walking boot, use of Charcot Restraint Orthotic Walker (CROW)
    - *Surgical treatment:* Surgery is recommended for those patients who have severe ankle and foot deformities that are unstable and at high risk of developing a foot ulcer. In addition, if the deformity makes braces and orthotics challenging to use, surgery may be indicated. After surgery, the patient will have to avoid putting full weight on the Charcot's foot for an extended period.
    - Danosumab may be considered along with TCC to reduce the risk of fractures in acute Charcot Foot. However, Teriparatide has not been shown to reduce time to remission or fracture risk.
- COVID-19 and its impact
  - COVID-19 is associated with an increased risk of thrombotic complications including the peripheral ischemic foot. It needs heightened screening with ABI in patients with a history of COVID-19.
- Diabetic patients with the risk or history of stroke:
  - Pioglitazone may be effective for secondary prevention in patients with stroke/transient ischemic attack.

Risk classification level	Management
No added risk: No risk factors; no previous history of foot ulcer or amputation	Provide structured foot-care education and annual review.
At risk: One risk factor; no previous history of foot ulcer or amputation	• Foot-care team to regularly review every 6 months. • At each review: - Inspect both feet - ensure provision of local management as indicated - Educate patient to wash feet daily (with careful drying, particularly between the toes), use emollients to lubricate dry skin, cut toe nails straight across, and avoid using chemical agents or plasters or any other technique to remove callus or corns - Evaluate footwear - provide appropriate advice - Enhance foot-care education
High risk: ≥2 risk factors; previous ulcer or amputation (very high risk)	• Foot-care team to frequently review every 3-6 months. • Educate patient to self-monitor foot skin temperatures once per day to identify any early signs of foot inflammation to prevent a first or recurrent plantar foot ulcer. • At each review: - Inspect both feet - ensure the provision of local management as indicated - Evaluate footwear - provide advice and specialist insoles and shoes if indicated - Consider the need for vascular assessment or referral, if indicated - Evaluate and ensure appropriate provision of intensified foot-care education

Limited Care
• Risk assessment and classification: Similar to 'recommended care' but with sensory assessment by 10 g monofilament or tuning fork, with or without non-traumatic disposable pin-prick only, and peripheral circulation assessment by palpation of pedal pulses. • NSS and NDS in T2DM population have been found to be a useful resource and an essential bed-side tool in evaluating diabetic sensorimotor polyneuropathy. • Classification of infection: Similar to 'recommended care', but antibiotic therapy would be with generic penicillin, quinolones, macrolides and/or metronidazole, given intravenously for deep tissue infections adjusted by response or culture results. • Vascular referral would be according to findings and local revascularization facilities.

Background

Peripheral neuropathy, peripheral vascular disease (PVD), if it occurs only in the arteries, is called PAD, gait disorders, ischemia, foot ulcers, infections, gangrenes, Charcot neuroarthropathy, and lower extremity amputations are some of the lower limb complications observed in patients with diabetes[557,558]. Lack of sanitation and hygiene, socio-cultural practices such as barefoot walking indoors and at religious places, walking on fire, a lack of awareness on the use of proper footwear, and a dearth of foot care clinics, together with economic factors exacerbate diabetic foot complications in India[559,560].

Diabetic foot ulcers and peripheral arterial disease

In India, DFUs [Figure 10] affect 25% of total diabetic patients during their lifetime and are one of the most common reasons for hospitalization and amputation. The cost of diabetic foot care in India is among the highest in the world[561] (~5.7 years of average annual income).

Neuropathy and PVD are important risk factors in diabetic foot infections[562–564] that are a significant cause of amputation and mortality amongst patients with diabetes in India[565,566]. While the prevalence of neuropathy has been estimated to be ~15%,[567] PVD prevalence varies across geographies. A lower prevalence has been reported among Indians compared to Western countries (13% versus 48%);[568] a younger patient population, a shorter lifespan of patients with diabetes, and a lower proportion of smokers could be plausible reasons for this difference.[564,568,569]The presence of PVD and claudication in patients with diabetes indicates PAD, leading to a higher risk of cardiovascular mortality and morbidity.[487] Recently, COVID-19 has been associated with an increased risk of thrombotic complications, including the peripheral ischemic foot. It needs heightened screening with ABI in patients with a history of COVID-19.[570,571] Despite the prevalence of PAD being estimated to be 50- 60% amongst patients with DFU, appropriate and timely diagnosis of PAD [Figure 10] is still a major concern and a leading cause of amputation in patients with diabetes[572] .

Charcot neuroarthropathy

The Charcot neuroarthropathy is a major consequence of diabetic neuropathy that leads to bone deformities, subluxation, and dislocation resulting in inflammation characterized by a reddish, hot, swollen foot: the Charcot's foot. The classic "rocker-bottom" foot is an example of an end-stage disease with severe fracture dislocation, the collapse of the midfoot, dorsal dislocation of the metatarsals, and plantar dislocation of the tarsal bones.[573–575] The prevalence ranges from 0.4%-13% among patients with diabetes, with a mortality rate of 28%. Using X-ray and MRI, the detection rates increase to ~30% and 75%, respectively.[574]

Diagnosis of Charcot's foot is often delayed or missed and can lead to severe foot deformity, ulceration, infection and/or lower extremity amputation.[575] Initial diagnosis includes testing for sensory neuropathy done using a 128-Hz tuning fork, a 10-g monofilament, or by testing light-touch perception. Treatment is primarily conservative, with early treatment options being off-loading with total contact casting (TCC) and non-weight bearing in a cast or wheelchair until the acute inflammatory process subsides (may take weeks or months). A prefabricated orthosis device such as a Charcot Restraint Orthotic Walker (CROW) may also be used. Overall, the fixation period depends on reduced edema and a drop in skin temperature below 2°C compared to the contralateral extremity. Late treatment requires reconstructive surgery to repair the deformity and obtain a plantar-grade foot. Off-loading using therapeutic footwear that off-loads the foot by at least 30% may be associated with a lower risk of recurrence.[573]

Diabetic foot infections

Compared to non-diabetics, patients with diabetes are more susceptible to infections due to their impaired inflammatory response, inferior wound healing owing to inadequate phagocytic clearance, increased oxidative stress, and down-regulation of different growth factors resulting in defective angiogenesis.[576] The Infectious Diseases Society of America (IDSA) recommends that the antibiotic regimen in patients with diabetic foot infections should be based upon culture and susceptibility analysis[577]. Additional therapies may include antibiotic impregnated beads, negative pressure wound therapy (NPWT), and hyperbaric oxygen [Figure 11][578]. In 2014, The Society for Vascular Surgery (SVS) published the Threatened Limb Classification System [Figure 13], based on three major risk factors associated with limb amputation: Wound, Ischemia, and foot Infection (WIfI)[579].

Strategies aimed at preventing foot diseases are cost-effective and can even be cost-saving if increased education and efforts are focused on those patients with recognized risk factors for the development of foot problems. The management of diabetic foot disease may seem poorly defined by comparison with complications such as nephropathy, hyperlipidemia and retinopathy, for which clear guidelines exist. A multidisciplinary team approach, particularly in specialized diabetic foot clinics, can reduce the burden of diabetic foot complications in developing countries like India. Patients not conforming to the foot care advice suffer and develop new problems and/or require surgical procedures.[580]The present guideline focuses on the various mechanisms of managing diabetic foot disease.

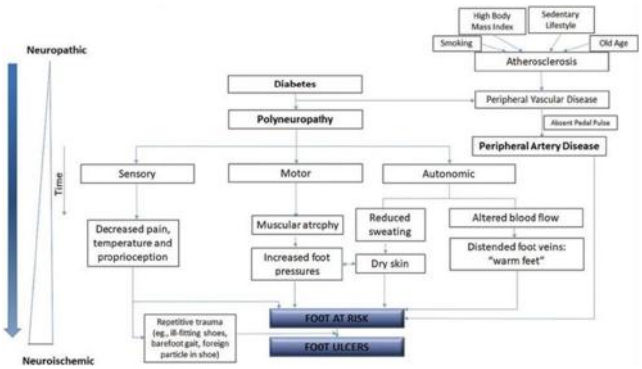


Figure 9: Pathogenesis of diabetic foot ulcer. Adapted from Boulton *et al*., 2018[573].

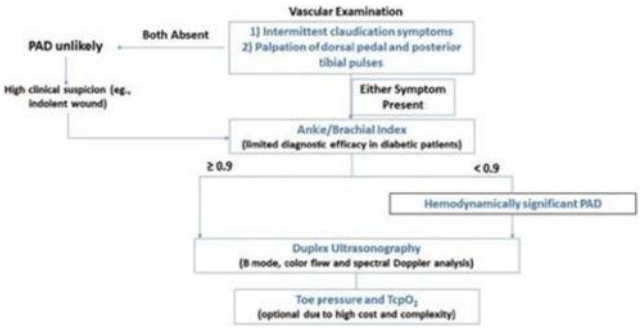


Figure 10: Vascular examination for PAD diagnosis. Adapted from Boulton *et al*., 2018;[573] PAD: Peripheral artery disease; TcpO2: Transcutaneous oximetry

Considerations

Identifying a diabetic patient at-risk of a foot ulcer is an important step in the timely management of future complications. The panel recommended IWGDF 2019[581] risk stratification system for risk assessment and the corresponding frequency of foot screening and examination [Table 17].

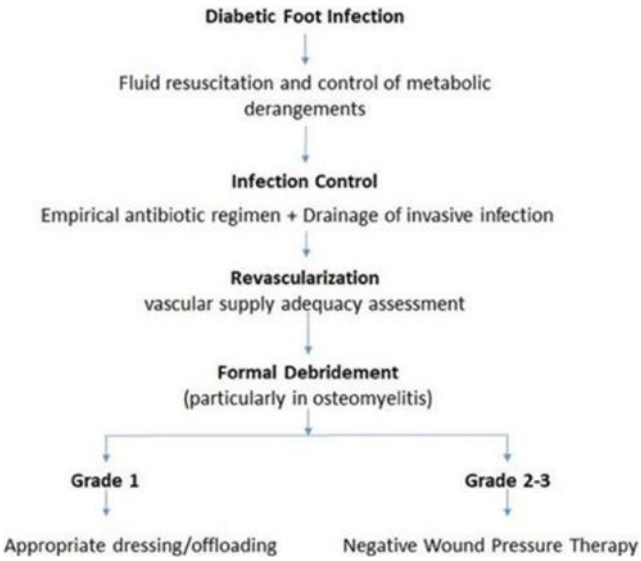


Figure 11: Diagnosis and management of diabetic foot infection. Adapted from Boulton *et al*., 2018.[573] MDRO: Multi-drug Resistant Organism;

NWPT: Negative Wound Pressure Therapy

The panel endorsed the IDF 2017 recommendations for the diagnosis and management of diabetic foot complications. However, few recommendations were modified based on local factors such as limited resources and lack of quality assurance in laboratories, which were reviewed in an Indian context.

Table 17: IWGDF risk stratification

IWGDF risk category	Ulcer risk	Characteristics	Frequency (adapted for the Indian population)
0	Very low	No LOPS and no PADS	Once every 12 months
1	Low	LOPS or PAD	Once every 6-12 months
2	Moderate	LOPS + PAD or LOPS + foot deformity LOPS + foot deformity	Once every 3-6 months
3	High	LOPS or PAD + one or more of the following: History of foot ulcer A lower-extremity amputation (minor or major) End-stage renal disease	Once every 1-3 months And at every visit to the doctor

Adapted from International Consensus on the Diabetic Foot 2019.[581] LOPS: Loss of protective sensation, PAD: Peripheral artery disease

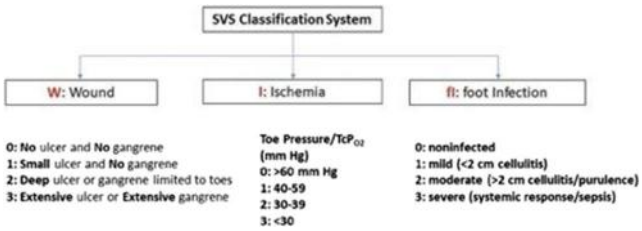


Figure 12: Threatened limb classification system. Adapted from Mills *et al*., 2014;[579] SVS: Society for vascular surgery

Rationale And Evidence

Detection and timely screening

- Vibration perception threshold (VPT) is considered as a gold standard for the diagnosis of diabetic peripheral neuropathy. However, the use of simple clinical scores such as NSS and diabetic neuropathy examination (DNE) scores were found to be valuable tools for the diagnosis of peripheral neuropathy in patients with diabetes.[582,583] Moreover, a good correlation between VPT score with a tuning fork, monofilament, and ankle reflex was found, suggesting that simple bedside tests are useful in clinical practice, even in those in whom foot care practices are not followed[584,585].
- Using NSS and NDS in T2DM patients has been found to be a useful resource in evaluating diabetic sensorimotor polyneuropathy as an important bed side tool.[586–588]
- Graduated RydelSeiffer tuning fork has a high specificity and a fairly good sensitivity in diagnosing diabetic foot problems.[589]
- Tip-therm, a device that tests for temperature discrimination, was compared with two validated methods for detecting neuropathy-a monofilament and biothesiometry in a study comprising 910 diabetic patients. Tip-therm was found to be an inexpensive, highly sensitive, and specific device for the detection of diabetic neuropathy when compared with biothesiometry and a monofilament[590].
- Evidence suggests that abnormal plantar foot pressure may exist in diabetic patients before there is evidence of neuropathy (determined by biothesiometry and monofilament tests). Podotrack, a novel, the inexpensive method can be used as a screening test for abnormal plantar foot pressure in this patient population[591].
- Gait variations and restrictions in the subtalar and first metatarsophalangeal joint have been reported in cases of diabetic neuropathy even before the onset of foot deformity. They could be used as an aid for early diagnosis[592].
- ABI and tcPO2 may be used as predictors of ulcer healing and amputation, respectively; ABI = 0.6 was found to have 100% sensitivity and 70% specificity and tcPO2 = 22.5 was found to have 75% sensitivity and 100% specificity in predicting wound healing.[593]

Avoid walking barefoot

- Sociocultural practices like barefoot walking indoors and in other religious places, use of improper footwear, and lack of knowledge regarding foot care are significant contributors to diabetic foot complications in India.[567,594] Therefore, the panel emphasized educating patients on problems associated with walking bare foot[595] and advice on using appropriate/therapeutic footwear, particularly for those at high-risk to prevent the development of foot deformities and ulceration.[596]
- A questionnaire-based study evaluating the foot care knowledge and practices with foot complications in 300 Indian patients suggests that most were not previously educated about foot care and walked indoors without footwear. The study emphasized that poor knowledge of foot care and poor footwear practices are important risk factors for foot problems in diabetes. It called for a joint effort from doctors and the footwear industry to educate patients about foot care and improve their choice and selection of footwear to reduce foot problems[597].

Management of diabetic foot complications

- MRI has emerged as the most accurate method of diagnosing bone infection, but bone biopsy for culture and histopathology remains the criterion standard[598]
- Neuropathy increases the risk of amputation 1.7-fold; 12-fold if there is deformity, and 36-fold if there is a history of previous ulceration.
- A phase 3 multicentre study has provided evidence to support the safety and efficacy of rhEGF formulated gel; the gel healed diabetic foot ulcers faster than treatment with placebo.[599]
- A peptide mimetic of the C-terminus of Cx43 (gap- junctional protein), alpha connexincarboxy-terminal (ACT1), when incorporated into the standard-of-care protocols, was found to be associated with a more significant percentage of participants achieving 100% ulcer re-epitheliazation and a reduced median time-to-complete-ulcer closure[600].
- Imipenem was found to be the most potent antimicrobial against both Gram-Positive Cocci and Gram-Negative Bacilli. Among combination therapies, cefepime-tazobactum and cefoperazone-sulbactum were the most effective. Antimethicillin-resistant *Staphylococcus aureus* (MRSA) antimicrobials such as linezolid and vancomycin and an anti-extended spectrum of beta-lactamase (ESBLs) like imipenem and meropenem can be given to patients producing MRSA or ESBL[601].

- Rivoraxaban is recommended along with the standard of care in patients with PAD (especially following revascularization) to reduce the incidence of adverse limb and cardiovascular events. Studies have also shown that Rivoraxaban for PAD is useful as well. [602–605]

Adjunctive treatment options

- In a small study comprising six patients with DFU, hyperbaric oxygen therapy showed a positive effect in initiating ulcer healing compared to standard treatments like offloading, wound debridement, and glucose control.[606]

Pressure off-loading

- Pressure modulation, commonly referred to as 'off-loading' is an important component in managing and treating diabetic foot ulcers. It involves mitigating pressure at an area of high vertical or shear stress[607,608]. Combining effective, easy-to-use off-loading devices such as total contact casts and removable cast walkers ensure patient compliance, healing foot ulcers, and avert limb amputations[608,609].
- Mandakini off-loading device[610,611] and Samadhan off- loading system[611,612] were found to be most economical, easy to apply and effective methods to re-distribute the pressure in ulcerative areas.
- A recent systematic review and meta-analysis report that compared with standard dressing changes, negative- pressure wound therapy had a higher rate of complete healing of ulcers (RR: 1.48; 95% CI: 1.24, 1.76; p<0.001), shorter healing time (MD:-8.07; 95% CI:-13.70,-2.45; p=0.005), greater reduction in ulcer area (MD: 12.18; 95% CI: 8.50, 15.86; p<0.00001), greater reduction in ulcer depth (MD: 40.82; 95% CI: 35.97, 45.67; p<0.00001), fewer amputations (RR: 0.31; 95% CI: 0.15, 0.62; p=0.001) and no effect on the incidence of treatment-related adverse effects (RR, 1.12; 95% CI: 0.66, 1.89; p=0.68)[613].
- The risk of amputation increases with increasing severity and location of the deformity and complexity/stage of Charcot neuroarthropathy, as per Roger's Charcot foot classification system.[614]
- Patients who use therapeutic footwear have demonstrated lower foot pressure, while those who use nontherapeutic footwear show an increased foot pressure, implying that therapeutic footwear is useful in reducing new ulceration and, consequently the amputation rate in the diabetic population[615].
- Patients with diabetic peripheral neuropathy and/ or prior foot ulcers report a higher incidence of falls than non-diabetics[616–618]. Specialty off-loading devices, decreased sensorimotor function, musculoskeletal/neuromuscular deficits and pharmacological complications are implicated as the high incidence observed. Novel technological advancements, such as virtual reality proprioceptive training, may help in reducing the risk of such falls.[617]

Medical Management of Charcot's foot

- In the trial by Das et al., to assess the effect of methylprednisolone (MP) or zoledronic acid (ZA) for resolution of active Charcot neuropathy (CN), it was observed that there was no added benefit of ZA for earlier remission of CN as compared with TCC alone, as previously documented. The strengths of this study include an intensive follow-up, a comparison of a potent anti-inflammatory agent (MP) with ZA and TCC, and a prospective analysis of BTMs and inflammatory markers. In conclusion, MP does not reduce time to remission in active CN of the foot despite the reduction in inflammatory cytokines.[619]
- Systematic review done on RCTs published in PubMed, EMBASE, SCOPUS and Cochrane Library from January 1994 to December 2019 showed that pharmacotherapy non significantly increased time to remission compared to TCC alone. A nonsignificant increase in BMC, a decrease in foot temperature, and alkaline phosphatase were observed with intervention. Limited evidence from available studies does not support the role of anti-resorptive or anti-inflammatory drugs for earlier remission when added to offloading with total contact cast for active CN of the foot. [620]
- Other studies include long-term foot outcomes following differential abatement of inflammation and osteoclastogenesis, charcot neuroarthropathy in diabetes mellitus, prevalence of mortality in Asian Indians with the same, and outcome analysis, with the efficacy of interventions such as teriparatide for diabetic chronic Charcot neuroarthropathy.[621–624]
- The role of Danosumab and Teriparatide for Charcot neuroarthropathy has been highlighted by Petrova et al. and Busch-Westbroek et al. [625,626]

Stroke

Rationale and Evidence

- Pioglitazone for primary stroke prevention in Asian patients with type 2 diabetes and cardiovascular risk factors. Compared with patients who did not receive pioglitazone, those who administered pioglitazone had a lower risk of developing ischemic stroke (adjusted hazard ratio: 0.78; 95% confidence interval: 0.62–0.95). The subgroup analyses defined by different baseline features did not reveal significant alterations in the observed effect of pioglitazone. Moreover, a significant decreasing trend in ischemic stroke risk with an increase in pioglitazone dose (p-value for trend = 0.04) was observed.[627]
- Pioglitazone is a potent insulin sensitizer, preserves beta-cell function, causes a durable reduction in HbA1c, corrects multiple components of metabolic syndrome, and improves non-alcoholic fatty liver disease/non-alcoholic steatohepatitis. Adverse effects (weight gain, fluid retention, fractures) must be considered, but are diminished with lower doses and are arguably outweighed by these multiple benefits. With healthcare expenses attributable to diabetes increasing rapidly, this cost-effective drug requires reconsideration in the therapeutic armamentarium for the disease.[628]
- In the Insulin Resistance Intervention After Stroke (IRIS) randomized clinical trial, pioglitazone, an insulin-sensitizing agent, reduced the risk for recurrent stroke or myocardial infarction (MI) among patients with insulin resistance. However, insulin resistance is not commonly measured in clinical practice.[629]

Implementation

Availability of basic equipment, appropriate protocols, structured records, and recall systems need to be supported by proper training for professionals providing screening and management services. Standard care of diabetic foot complications includes maintaining adequate vascular supply, preventing and treating soft-tissue and bone infection, performing initial excisional debridement and maintenance debridement as inducted, and adhering to high-quality off-loading. Liaison needs to be established with orthoptists, footwear suppliers, and cast technicians. Multidisciplinary management programs should be initiated focusing on prevention, education, regular foot examinations, aggressive intervention, and optimal use of therapeutic footwear.

DIABETES AND HEART

Recommendations

Recommended Care

- Cardiovascular risk factors that should be assessed in all patients at diagnosis and annually including
  - Dyslipidemia
  - Hypertension
  - Smoking status
  - Family history of premature coronary disease
  - Presence of albuminuria including micro-albuminuria >30 mg.
  - Body mass index (BMI) ≥25
  - Presence of hyperuricemia
  - Duration of diabetes
  - Screening for heart failure on the basis of **2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure.** [630]
  - Presence of retinopathy as it doubles the risk of CVD [631]
  - Sleep duration has also been added as a new parameter for CVD risk
- Current or previous CVD events, age, body weight, BP and pulse, of patients should be recorded during their first and subsequent visits
- UKPDS risk engine and QRISK3 are simple and effective tools for identifying and predicting CVD risks in patients with T2DM and should be recommended for identifying high risk individuals*
- Patients with diabetes and CVD risk should follow the ABC treatment goals**
  - A (HbA1c): <7%
  - B (BP): <130/80 mmHg
  - C (Cholesterol -LDL): <100 mg/dL
- CV Risk assessment is to be done in all type 2 diabetes patients with multiple risk factors.
- Primary prevention is important for those at risk of Heart failure (stage A) or pre HF(stage B)
- All patients should be managed with lifestyle intervention including physical exercise and medical nutrition therapy
- In high-risk patients, low dose aspirin therapy should be administered along with lifestyle intervention
- Statins should be added to lifestyle intervention in all patients with CVD risk, if not contraindicated. The intensity can be modified or titrated according to patient's CVD risk, age, side-effects, tolerability, LDL-C levels etc.
- Glycemic control with glucose lowering drugs that are proven to be CV safe and beneficial should be recommended to reduce CVD risk and complications in patients with T2DM. SGLT2 inhibitors and GLP-1 receptor agonists are approved by various regulatory authorities for CV risk reductions, apart from their glucose lowering ability.
- Weight control should be an important consideration, while choosing glucose lowering therapy in overweight/obese persons
- Pharmacological antihypertensive therapy with subsequent titration in addition to lifestyle therapy should be initiated in patients with confirmed office-based BP of >140/90 mmHg
- Pharmacological therapy for patients with diabetes and hypertension should comprise a regimen that includes ACE inhibitor/ARB, thiazide diuretics, calcium channel blockers, and selective β blockers. If one class is not tolerated, it should be substituted with molecules from other classes; however, FDCs of different drug classes may be preferred in patients with diabetes to reduce CVD risks and complications and increase compliance.
- ACE inhibitors are the drug of choice for diabetes, if not contraindicated; and ARBs may be used if ACE inhibitors are not tolerated
- Other medications for dyslipidemia (fibrates, ezetimibe, concentrated omega-3 fatty acids, PCSK9 inhibitors, Bempedoic Acid-Recommended DCGI Approved) can be considered in patients failing to reach targets with conventional lipid lowering medications

*The treatment target goals should be individualized according to age, risk and comorbidity. **Risk factor: Low-density lipoprotein (LDL)-cholesterol ≥100mg/dL (2.6 mmol/L), high blood pressure (> 140/90 mm Hg), smoking, overweight/obese, lack of physical activity

Limited Care

- Cardiovascular risk factors like albuminuria and hypertension should be assessed in all patients at diagnosis and annually
- Cardiovascular risk may be calculated by using different assessment tools for people with diabetes as recommended

Background

Patients with T2DM are always at higher risk for several CVDs such as CAD, CHF,(both HFpEF,HFrEF), stroke, PAD, and dilated cardiomyopathy (DCM). Furthermore, compared to patients without diabetes, T2DM patients have a considerably higher risk of CV morbidity and mortality.[632] In addition, the coexistence of risk factors like hypertension, dyslipidemia, obesity and smoking with T2DM may increase the burden and complications of CVD.[633] In India, CVD attributes to nearly 25% of all deaths. Apart from increasing age and obesity, diabetic people have a 33% greater risk for hospitalization for HF. Even individuals with PD have a 9-58% greater risk to develop HF with an extended risk for all cause mortality and cardiac outcomes as per a recent review.[634] Furthermore, according to the Global Burden of Disease study, age-standardized CVD mortality rate was 272 per 100000 population in India, which was higher than the global average of 235 per 100000 population.[635] An Indian population-based study in 6198 patients with T2DM that evaluated the prevalence of CVD risk factors reported that, compared to participants with diabetes versus those without it, prevalence of hypertension was 73.1% (95% CI: 67.2 to 75.0) vs 26.5% (25.2 to 27.8), hypercholesterolemia was 41.4% (38.3 to 44.5) vs 14.7% (13.7 to 15.7), hypertriglyceridemia was 71.0% (68.1 to 73.8) vs 30.2% (28.8 to 31.5), low HDL-C was 78.5% (75.9 to 80.1) vs 37.1% (35.7 to 38.5), and incidence of smoking/smokeless tobacco use was 26.6% (23.8 to 29.4) vs 14.4% (13.4 to 15.4; $p<0.001$).[636] *

Several landmark studies have reported that patients with T2DM are at increased risk for several cardiovascular complications. A brief overview of the CINDI studies, INTEHEART and INTERSTROKE is presented in Table.[637–640] Therefore, aggressive control of these risk factors may delay or reduce the incidence of CVDs in T2DM patients.

Considerations

When framing recommendations for diabetes and CV risk, following factors should be reviewed: hypertension, smoking, obesity, increased fasting insulin and Insulin Resistance (IR), lifestyle intervention, atherogenic lipid profile (abnormal cholesterol, high triglycerides, high LDL-C).

Primary prevention of CVDs aims at preventing patients from the event of CHD/CVD. This includes engaging in moderate physical activity, maintaining normal body weight, limiting alcohol consumption, reduction of sodium intake, maintaining adequate intake of potassium, and consumption of a diet rich in fruits, vegetables, and low-fat dairy products with less saturated and total fat. Secondary prevention of CVDs in patients with diabetes plans to reduce the mortality and morbidity and prevent the repeated CVD event. This comprises treatment with aspirin, β-blockers, ACE inhibitors and statin. The tertiary prevention intends at rehabilitation, preventing complications, and improving QoL. This can be achieved with some interventional surgical procedures. Quaternary prevention targets at preventing over diagnosis, over medicalization, over labeling and over treatment.

Rationale and Evidence

Identification

Cardiovascular risk factors such as dyslipidemia, hypertension, smoking, high body-mass index (BMI), family history of premature coronary disease and the presence of albuminuria and hyperuricemia should be assessed at least annually in all patients with T2DM.[633,641,642] Even the CINDI and CINDI 2 studies in Indian population recommend screening of CV complications at the time of diagnosis.[637,638]

The following tools have been used by several physicians for assessment of the CVD risk in individuals with diabetes and CVD.

- QRISK3 Risk Score[643,644]
- UKPDS Risk Engine.[645]

Recently, the DISCOVER observational study (N=15,992) has been initiated to collect real world data from 38 countries to understand patterns of T2DM care in patients who initiated a second-line glucose-lowering therapy. Data from several lower-middle and upper-middle income countries collected for the first time through DISCOVER revealed that 26.7% of the patients Across Region Range (ARR) had HbA1C >9%, with highest populations in South-East Asia (35.6%) mostly attributed to low education level, low country income and larger time in initiation of second line therapy.[646]

Table 18: Studies assessing cardiovascular risk factors

Study characteristic	CINDI (India, 2014)	CINDI 2 (India, 2016)	INTERHEART (Global, 2004)	INTERSTROKE (Global, 2016)
Study population	4600 newly diagnosed patients with T2DM (men: 67%)	1500 newly detected young-onset diabetes patients (men: 74%)	15,152 cases with acute MI, 14,820 controls from 52 countries	13,447 cases (10,388 with ischemic stroke and 3059 intracerebral hemorrhage) and 13,472 controls from 32 countries (men: 59.6%)
Study objective	To assess patients for diabetic complications, hypertension, dyslipidemia, BMI, diagnosis of retinopathy, neuropathy and nephropathy	To evaluate patients for complications of diabetes and CV risk factors such BMI, hypertension, dyslipidemia, and smoking	To assess relationship between smoking, history of hypertension or diabetes, WHR, dietary patterns, physical activity, consumption of alcohol, blood Apo, and psychosocial factors to MI	To assess relationship between stroke and its risk factors including hypertension, physical activity, ApoB/ApoA1 ratio, diet, WHR, psychosocial factors, current smoking, alcohol consumption and diabetes
Results overview	Hypertension, obesity and dyslipidemia were present in 23.3%, 26% and 27% patients, respectively	Hypertension, dyslipidemia, BMI >23 kg/m^2, and smoking were present in 27.6%, 62.4%, 84.2 and 24% patients. Diabetic retinopathy, neuropathy, and nephropathy were seen in 5.1%, 13.2%, and 0.9%. Ischemic heart disease, PVD, and stroke were presented in 0.7%, 2%, and 0.1%. 95.33% needed statin therapy	Diabetes, along with smoking raised ApoB/ApoA1 ratio, history of hypertension, abdominal obesity, psychosocial factor, lack of daily consumption of fruits and vegetables regular alcohol consumption, and lack of regular physical activity were all significantly related to acute myocardial infarction (P<0.0001 for all risk factors and)	Previous history of hypertension or BP of 140/90 mm Hg or higher, regular physical activity, WHR, psychosocial factors, smoking, cardiac causes, alcohol consumption and DM were all associated with stroke. Hypertension was more associated with intracerebral hemorrhage than with ischemic stroke, whereas current smoking, diabetes, Apo, and cardiac causes were more associated with ischemic stroke (P<0.0001)

DM: Diabetes mellitus, Apo: Apolipoproteins, BMI: Body mass index, MI: Myocardial infarction; T2DM: Type 2 DM, PVD: Peripheral vascular disease, WHR: Waist-to-hip ratio, BP: Blood pressure

Management

Lifestyle intervention

Early identification of metabolic syndromes such as AO, elevated BP, hypertriglyceridemia, reduced HDL cholesterol, borderline high-risk LDL cholesterol and IFG (110 to 126 mg/dL) and design interventions to reduce the CVD risks are the major goals of the primary prevention.[647] Furthermore, close monitoring and maintaining recommended targets for BP (130/80 mmHg), lipid control (LDL <100 mg/dL), and glycaemia (A1C <7%) is important for the prevention of CVD in patients with T2DM.[647,648] In addition, physical exercise, weight control, lifestyle modification with changing food habits, and cessation of smoking also prevents the CVD risk in T2DM patients.[647]

- Diet: In the PURE study (N=135,335), a diet rich in carbohydrates was shown to be associated with higher risk of total mortality. Surprisingly, both, total fat and individual fat type were not correlated with CVD, CVD-related mortality or MI. In fact, saturated fat had an inverse correlation to stroke.[649]Therefore, a high carbohydrate intake is a potent risk factor of CVD and mortality. Current nutritional recommendations for patients with T2DM propose restricting the total carbohydrate intake to ~45-50% of the total energy. Moreover, there is increased focus on the quality of carbohydrate intake, with an emphasis on including complex carbohydrates like brown rice and whole grain wheat into the diet.[650]
- Substitution of dietary saturated fat with PUFAs is reported to be associated with improved CV outcomes. Moreover, American Family Physicians (AFP) advocates that the Mediterranean diet can reduce CV mortality and the DASH eating plan is associated with a reduced risk of CHD.[651] Moreover, the following dietary adaptations can be made to lessen the development of CVDs in T2DM patients: reductions in caloric intake (by 500 kcal/day to 800 kcal/day), total fat intake (especially saturated fat) and food portion sizes, increased consumption of dietary fiber, and moderate alcohol use.[652]
- Physical activity: It is an independent and protective risk factor associated with reduced CV morbidity and mortality (OR, 0.86; p<0.0001), and physical inactivity accounts for 12.2% of the population-attributable risk for acute MI and 6% of CHD with an estimated 0.68 year reduction in life expectancy.[651] The exercise- based cardiac rehabilitation (CR) is the cornerstone for secondary prevention of CVD. CR is associated with a 13% and 26% lower all-cause and CVD mortality, respectively and a 31% reduction in hospital admissions at 12 months in patients with CHD.[651]
- Stress management: Evidence state that psychosocial stress has an association with the etiology and pathogenesis of CVDs.[653] Most notably, the INTERHEART and INTERSTOKE studies report that psychological factors have a strong effect towards MI (OR: 2.67, PAR 32.5%, p<0.0001) and ischemic stroke (OR: 2·20, 1·78, 2·72; 17·4%, 13·1, 22·6) respectively.[639,640] In an RCT, cognitive behavioral therapy (CBT) had a 41% lower rate of fatal and non-fatal first recurrent CVD events (HR:0.59; 95% CI: 0.42,0.83; p=0.002), 45% fewer recurrent acute MI (HR: 0.55, 95% CI: 0.36, 0.85; p=0.007), and a non- significant 28% lower all-cause mortality (HR: 0.72, 95% CI: 0.40, 1.30; p=0.28) than the reference group after adjustment for other outcome-affecting variables during a mean 94 months of follow-up period.[654] Nonetheless, a recent Cochrane review did not find such associations of CVD events with the psychological interventions in CHD patients.[655]

Pharmacological management

- Medical treatment with pharmacotherapies like aspirin, lipid lowering drugs and BP controlling agents improves survival, extends QoL, reduces the need for intervention procedures, such as angioplasty and coronary artery bypass graft surgery, and decreases the incidence of subsequent MI.[656]

Antiplatelet therapy

- Aspirin is widely used for secondary prevention of CVD however; its use in primary prevention is still controversial.[534] In the recent ASCEND study, aspirin use prevented serious vascular events in patients with diabetes with no evident cardiovascular disease at trial entry. However, these preventive benefits were counterbalanced with major bleeding hazards.[657] Furthermore, a meta- analysis demonstrated 35% reduction in MI among men (RR: 0.65; 95% CI: 0.51,0.82; p<0.01), but the results were not significant in women (RR: 0.90; 95% CI: 0.71, 1.14; p=0.37).[658]However, a systematic review including 10 RCTs reported no CVD benefit and trials with diabetes subgroup analyses also did not show any effect.[659] Similarly, a recent meta-analysis evaluated aspirin for primary prevention of CVD in patients with diabetes and reported no difference with respect to the risk of all- cause mortality (OR: 0.93, 95% CI: 0.81, 1.06), individual atherosclerotic events, bleeding, gastrointestinal bleeding, or hemorrhagic stroke rates compared to placebo.[660] Furthermore, a meta-analysis (n = 4000) by the Antithrombotic Trialists' (ATT) collaborators showed that the effects of aspirin on major vascular events were similar for patients with or without diabetes: (RR: 0.88, 95% CI: 0.67, 1.15) and (RR: 0.87, 95% CI: 0.79, 0.96) respectively.[661]
- Based on cumulative data, the US Preventive Services Task Force (USPSTF) updated its 2016 recommendations on the use of aspirin for the primary prevention of CVD. The 2022 USPSTF recommendations suggest that the decision to initiate low-dose aspirin for the primary prevention of CVD in adults aged 40 to 59 years who have a 10% or greater 10-year CVD risk should be an individual one (C statement), and recommends against initiating low-dose aspirin use for the primary prevention of CVD in adults aged 60 years or older (D statement). In patients with aspirin intolerance/allergy or patients at very high-risk for CVD, clopidogrel is recommended[633,662] Evidence suggests that clopidogrel was significantly more effective than aspirin in secondary prevention of CVD in patients with diabetes.[662] Furthermore, dual antiplatelet therapy may be reasonable for up to a year after ACS.[633]
- A Cochrane systematic review report demonstrated that use of clopidogrel plus aspirin was associated with a reduction in the risk of CV events and an increased risk of bleeding compared with aspirin alone. However, only in patients with acute non-ST coronary syndrome, benefits outweigh harms.[663]

Lipid lowering agents

- A high prevalence of lipid abnormality in patients with T2DM positions them at high risk category in the CVD risk stratifications. Elevated levels of atherogenic cholesterol (AC), generally measured as non HDL-C, plays a central role in CVD, especially among Asian Indians.[664]
- For management of dyslipidemia, the primary goal is to reduce LDL-C levels to <100 mg/dL by addition of drug therapy (statins) to maximal diet therapy. Furthermore, fibrates may be added if triglycerides remain >200 mg/dL in patients receiving statin therapy.[656] Statins reported a significant benefit in CV risk reduction and showed significant primary and secondary prevention of CVD/CAD deaths in patients with diabetes.[665–667]
- A recent meta-analysis investigating 4,351 diabetes patients reported that compared with placebo, standard-dose statin treatment resulted in a significant RRR of 15% in the occurrence of any major CV or cerebrovascular event (RR: 0.85, 95% CI: 0.79, 0.91). Compared with standard- dose statin treatment (simvastatin 20 mg, pravastatin 40 mg or atorvastatin 10 mg), intensive-dose statin (simvastatin 80 mg or atorvastatin 80 mg) treatment resulted in an additional 9% RRR.[668]
- Moreover, statins were reported to produce similar results in various studies in India.[669,670] Evidence advocates atorvastatin has negligible or no ability to increase HDL-C, which is the key feature in patients with diabetes. Thus, other statins should probably be preferred to atorvastatin in patients with diabetes/MS. [671]
- In addition ADA recommends that, either high intensity or moderate intensity statin therapy should be used together with lifestyle intervention according to patient age and ASCVD risk factors. [3,633]The details have been given in Annexure 6. The Lipid Association of India expert consensus statement 2016 revealed that statin therapy is highly effective in lowering Non-HDL-C, LDL-C, apolipoprotein B, and remnant cholesterol, besides being remarkably safe.[672] Recent evidence shows a clear CVD benefit of lowering LDL-C with ezetimibe on top of a statin in patients with T2DM.[673]
- Furthermore, in CHD/CHD risk-equivalent patients ezetimibe addition onto simvastatin, atorvastatin, or rosuvastatin provided greater LDL-C reductions and goal attainment than up-titrating statin therapies.[674] The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study assessed the effect of fenofibrate on CV events in T2DM patients. Fenofibrate reduced total CV events, mainly due to fewer non-fatal MI and revascularizations but, did not significantly reduce the risk of coronary events such as CHD death or non-fatal MI.[675] But the recent ACCORDION Study done on the surviving patients (N=853) of the ACCORD study continued fenofibrate, claimed that the incidence rate in the fenofibrate group were lower with respect to all-cause mortality (ACM) CVD-mortality, Non-fatal MI,CCF and major Coronary Events than placebo in the post-trial group. Allocation to combined statin and fenofibrate showed a beneficial effect on ACM by 35% (Adjusted HR=0.65; 95% CI-0.45-0.94; P=0.02).[676]
- Furthermore, USFDA states that the current evidence base is insufficient to support fibrates for CVD protection and that more trial evidence is needed.[677] Nonetheless, prescribing lipid-lowering agents in older people with T2DM (>85 years) requires special consideration because exposure to higher doses (or higher potency) might increase the risk of adverse effects instead of improving life expectancy. As per LAI guidelines too, fibrates should be added when the TG level goes above 500 mg/dl.
- Proprotein convertase subtilisin/kexin type 9 (PCSK9) regulates degradation of LDL-receptors (LDLR). PCSK9 inhibitors, such as evolocumab and alirocumab, have been shown to enhance recirculation of LDLRs to the surface of hepatocyte cells and accelerate clearance of circulating LDL-C. PCSK9 inhibitors can prove to be a valuable treatment option for statin-intolerant patients.[678]

Glucose lowering drugs

- Intensive glycemic control with antidiabetic drugs [Table 1] reduces CV risk and complications in patients with T2DM. A meta-analysis including large, long-term prospective RCTs (such as the UKPDS, the prospective pioglitazone clinical trial in macrovascular events [PROactive], the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE] trial, the Veterans Affairs Diabetes Trial [VADT] and the Action to Control Cardiovascular Risk in Diabetes [ACCORD] trial) report that intensive glycemic control was associated with 17% reduction in events of nonfatal MI (OR 0.83; 95% CI: 0.75–0.93), and a 15% reduction in events of CHD (OR, 0.85; 0.77–0.93); however the study did not find any significant effect on events of stroke (0.93, 0.81–1.06) or all-cause mortality (1.02, 0.87–1.19).[679]
- DPP4, dipeptidyl peptidase 4; GIP, gastric inhibitory polypetide; GLP-1, glucagon-like peptide-1;SGLT2, sodium-glucose transport protein 2.
- In a meta-analysis of 301 clinical trials, the CVD risk of all glucose-lowering drugs including; metformin, sulphonylurea, thiazolidinedione, DPP4 inhibitor, AGI, SGLT2 inhibitors, GLP-1 analogue, meglitinides, and insulins, were evaluated. The results indicated that there were no significant differences in the association between any of the nine glucose-lowering drugs alone or in combination and risk of CV mortality.[680]
- SGLT2 inhibitors, empagliflozin, canagliflozin, and dapagliflozine were recently shown to provide CV benefits in patients with T2DM. Empagliflozin was reported to produce substantial reductions in CVD death (38%) and all-cause mortality (32%), as well as in hospitalization for HF (35%), as compared with standard-of-care in EMPA- REG OUTCOME trial.[232] In the recently published CANVAS trial, canagliflozin significantly reduced the composite of death from CV

causes, non-fatal MI, or nonfatal stroke (HR, 0.86; 95% CI, 0.75 to 0.97; p<0.001 for non-inferiority; p=0.02 for superiority) in T2DM patients with established CVD or at high risk for CV events.[232]
- Similarly DECLARE also showed similar benefits with dapagliflozine in type 2 diabetes with low CV risk.
- GLP 1 analog CVOT LEADER trial, liraglutide 1.8 mg daily was associated with lower rates (patients) of death from CV causes (4.7% vs. 6.0%, HR, 0.78; 95% CI: 0.66 to 0.93; p=0.007) or any causes (8.2% vs 9.6%, HR, 0.85; 0.74 to 0.97; p=0.02) compared to placebo in patients with T2DM.[269] Therefore, using these medications early in the course of management in high risk T2DM patients could provide potential benefits from looming CVDs.
- All 3 SGLT 2 I are showing significant reduction in heart failure as a class effect. DAPA-HF[681]trial concluded that patients with heart failure with reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes. The EMPEROR trial showed that Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure reduced ejection fraction and a preserved ejection fraction, regardless of the presence or absence of diabetes.[682]

Recent 2022 AHA/ACC/HFSA Guidelines recommend following
1. HFrEF SGLT 2 I are must as one of 4 essential medicines
2. HFmrEF SGLT 2 I class of recommendation 2a
3. New recommendations for HFpEF are made for SGLT 2 I 2a

- Furthermore, recently released top-line results from the, CAROLINA trial (NCT01243424) showed that linagliptin was comparable to glimepiride vis-à-vis their impact on CV morbidity and mortality in patients with T2DM, after a median follow-up of 6.3 years.[683]
- In the SAVOR-TIMI 53 trial where patients were either randomized to saxagliptin or placebo, treatment with saxagliptin was associated with a 27% increased relative risk of hospitalization for heart failure in patients assigned to saxagliptin.[224] The risk was highest in patients with elevated levels of natriuretic peptides, previous heart failure or chronic kidney disease.[684]
- Except saxagliptin, other DPP- 4 inhibitors are cardiovascular neutral and therefore safe for the heart.[685]
- Major trials assessing the impact of glucose lowering agents in improving cardiovascular endpoints are schematically presented in Figure 14.

Blood pressure lowering agents.
- A tight control of BP with pharmacological therapy like ARBs, ACE inhibitors, or β-blockers, diuretics, and calcium channel blockers helps in minimizing CVD risks in patients with T2DM.[633]Tight control of blood glucose decreases the risk of microvascular complications, whereas tight control of BP reduces both micro-and macrovascular complications.
- ADA, IDF and other organizations recommends a target BP of 130/80 mmHg in diabetes patients.[264,633] Furthermore, patients with confirmed office-based BP >140/90 mmHg in addition to lifestyle therapy should be initiated with pharmacological therapy to achieve BP goals.[633]
- A meta-analysis including 147 RCTs involving 464,164 people report a significant reduction in risk of coronary events (20–25%) and stroke (30–45%) with all five BP lowering agents. However, calcium channel blockers had a greater preventive effect on stroke (RR 0.92, 95% CI: 0.85 to 0.98).[584]
- Two meta-analyses and ACCORD study reported that intensive BP control was associated with a reduction of stroke event, albeit with greater adverse effects.[686–688] In addition, in the ADVANCE trial, a fixed combination of perindopril and indapamide was associated with mean reduction in SBP of 5.6 mmHg and DBP of 2.2 mm of Hg after a mean of 4.3 years of follow-up in patients with T2DM. The relative risk of a major macrovascular or microvascular event was also reduced by 9%.[689]
- Furthermore, some patients require a combination of two drugs in order to achieve a recommended BP target. Several Indian studies evaluated the efficacy of some FDCs: losartan 50 mg plus ramipril 2.5 mg vs each alone,[690,691] metoprolol extended release (XL) plus amlodipine vs losartan plus amlodipine,[692] metoprolol and amlodipine,[693]and reported that the FDCs were effective, safe and well-tolerated in patients with hypertension.

Metabolic memory
Metabolic memory refers to the beneficial effects of early, intensive control of hyperglycemia, which can help reduce chronic complications of T2DM in later years. The STENO-2, EMPA-REG and LEADER trials have shown the positive effects of metabolic memory. Recent results of STENO-2 trial after 21 years follow-up reported that an intensive, multifactorial intervention including ACE inhibitors/ARBs demonstrated a median of 7.9 years of gain of life in patients with T2DM[694,695]The choice of individual agent for a person with diabetes may be influenced by a number of factors including their risk profile (CV, renal, end-organ damage), preferences, and previous experience of therapy, as well as costs.

Implementations
Patients with diabetes and CVD risk should be assessed for complete lipid profile and BP measurement during their medical visits. Antiplatelet agents, lipid lowering therapies, and antihypertensive medications along with lifestyle interventions should be provided with individualization and preference of each patient. Structured annual assessment and record-keeping should be instituted.

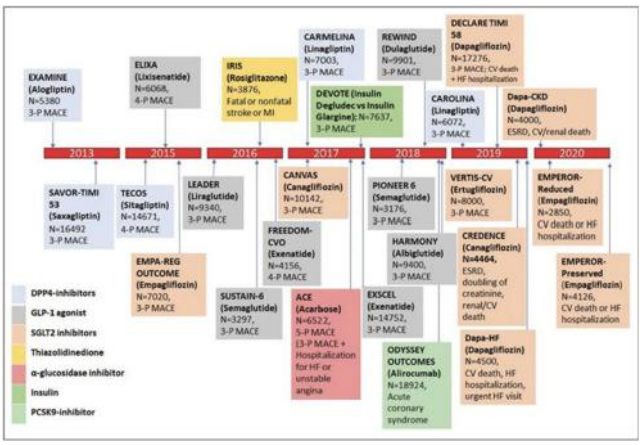


Figure 13: Major trials assessing cardiovascular outcomes in patients with diabetes. 3-P: 3-point; 4-P: 4-point; 5-P: 5-point. DECLARE-TIMI 58: Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; ESRD: End-stage renal disease; HARMONY Outcomes: Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus; PIONEER 6: A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes; REWIND: Researching Cardiovascular Events With a Weekly Incretin in Diabetes; VERTIS CV: Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease. Adapted from Cefalu *et al*., 2018[56]

Amplitude O trial- In this trial involving participants with type 2 diabetes who had either a history of cardiovascular disease or current kidney disease plus at least one other cardiovascular risk factor, the risk of cardiovascular events was lower among those who received weekly subcutaneous injections of efpeglenatide at a dose of 4 or 6 mg than among those who received placebo.[696]

OTHER COMPLICATIONS- BONE, SKIN AND HEPATOMEGALY

TYPE 2 DIABETES MELLITUS AND OSTEOPOROSIS

Recommended Care

Screening

- Screening for osteoporosis by ordering a DXA test should perhaps be more liberal in patient with diabetes (PWD). The IOF recommends that both men and women over the age of 50 should be screened. Since that seems impractical, we have suggested in our review that all over 60 should be screened, and those between 50 and 60 with at least 10 years diabetes duration should be screened. This is a suggestion and based on resource logistics, but also on the fact that the risk of fractures only increases after 5-10 years of diabetes. The point about screening must be emphasized so that more people with diabetes are evaluated for their bone health and measures instituted early rather than acting after the occurrence of fracture.[697–699]
- Treatment for osteoporosis in people with type 2 should be considered at a T score of -2 rather than -2.5
- Bone turnover markers are often "not high" and people with diabetes and must be interpreted with caution. The response of these markers to treatment is not altered - they will still reflect efficacy of treatment.
- If FRAX is used, Rheumatoid arthritis should be ticked as a risk factor in PWD since the risk conferred is about the same.

Initial first-line therapy for individuals with prevalent vertebral fractures

- Teriparatide is an effective anabolic agent to initiate therapy in these cases- to be continued for 24 months and followed by antiresorptive.
- Intravenous zoledronic acid or denosumab are also effective options. Since the protocol for discontinuing denosumab is still not firmly established, zoledronic acid is usually preferred as initial therapy for 3-5 years.
- Oral bisphosphonates can be used if the patient wants to avoid injectable therapies.

Initial first line therapy for individuals with prevalent hip fracture

- Intravenous zoledronic acid is the agent of choice in this group- it is recommended that hospitalized/post-surgical patients with hip fractures be given a dose of intravenous zoledronic acid before being discharged from the hospital.
- Denosumab is also an apt and effective choice but is often used after zoledronic acid, for reasons explained above.
- While teriparatide can be used in this situation, there is limited data available on the prevention of hip fracture

Recommendations for initial first-line therapy for high-risk individuals without prevalent fractures

- Bisphosphonates are generally agents of choice for those at high risk for fracture. While either weekly oral (alendronate, risedronate) or annual intravenous agents are effective, concerns about compliance and ease of once-a-year administration has made zoledronic acid the preferred drug for most patients. Both options should be discussed with the patient (weekly oral vs. annual intravenous) and treatment chosen accordingly. Denosumab can be used as a first choice too if the patient reacts to or wants to avoid bisphosphonates. Teriparatide can be considered for some with very low BMD (T score <-3.5) and high risk of vertebral fracture.
- The risk of rebound fractures is increased if subsequent doses of denosumab are not administered in time

Recommendations for initial first-line therapies for low and moderate-risk cases for vertebral, non-vertebral, and hip fractures

- Approved agents with efficacy to reduce hip, non-vertebral, and spine fractures include alendronate, risedronate, zoledronic acid, and denosumab, and these are appropriate as initial therapy for most patients at risk of fracture. Often oral bisphosphonates are preferred in low and moderate-risk cases.

Recommendations for the management of osteoporosis in chronic kidney disease (CKD) patients and those on dialysis

- Management of patients with osteoporosis and CKD is difficult as bisphosphonates are contraindicated in stage 4 and 5 kidney disease (eGFR below 30 to 35 ml/min). Denosumab is not cleared by the kidney and therefore can be used in these patients. However, the risk of hypocalcemia is high with this agent, especially in patients in stage 5 disease. Optimal calcium intake and vitamin D status should be assured before starting denosumab.
- A major concern with antiresorptive therapy in patients with CKD is adynamic bone disease and selected patients should undergo undecalcified iliac bone biopsy if facilities are available, to guide correct decision making for the management of osteoporosis.

Recommendations for HRT

- Although effective in increasing bone mass and prevent fractures, HRT is not recommended for managing osteoporosis due to high risk of side effects such cardiac events and breast cancer (although breast cancer risk is not increased with estrogens alone). HRT can be used when there is additional indication to use estrogens such as uncontrollable menopausal symptoms. In select cases (within the first 10 years after menopause in women without contraindications), HRT can be used for prevention of postmenopausal osteoporosis.
- Testosterone therapy may be added in androgen deficient men (testosterone level less than 200 ng/dL on more than one determination) if accompanied by signs or symptoms of androgen deficiency (e.g. low libido, unexplained chronic fatigue, loss of body hair, hot flushes, etc.) or "organic" hypogonadism (due to hypothalamic, pituitary, or specific testicular disorder). If testosterone treatment does not alleviate symptoms of androgen deficiency after 3–6 months, it should be discontinued, and other therapies considered. It should be noted that anti-resorptive and anabolic drug therapies are equally effective for osteoporosis in men as well.

Recommendations for intranasal calcitonin in the management of osteoporosis

- Intranasal calcitonin can be used for temporary bone pain relief. However, calcitonin's effectiveness in the prevention of osteoporotic fractures is very limited and should therefore be prescribed only in women who cannot tolerate bisphosphonates, denosumab, teriparatide, or raloxifene or for whom these therapies are not considered appropriate.

Recommendations for combination therapies

Combination therapy can be considered in patients with very high or imminent fracture risk. The use of teriparatide and denosumab has been shown to result in a great increase in BMD as against either agent alone. However, fracture prevention data are not yet available.

Recommendations for sequential therapies

- Treatment with teriparatide should always be followed by antiresorptive agents to prevent bone density decline and loss of fracture efficacy. Either bisphosphonates or denosumab can be used in this setting.
- In patients unresponsive to anti-resorptive therapy alone, treatment can be followed by a combination of teriparatide and anti-resorptives.
- Treatment with denosumab, if it has to be discontinued, should be followed by bisphosphonate, either zoledronate or alendronate in patients with adequate renal function. Delay in denosumab therapy or lack of another therapy 6 months after last denosumab dose is associated with a rebound increase in fractures.

Recommendations for initial first-line therapy for high-risk individuals without prevalent fractures

- Bisphosphonates are generally agents of choice for those at high risk for fracture. While either weekly oral (alendronate, risedronate) or annual

intravenous agents are effective, concerns about compliance and ease of once-a-year administration has made zoledronic acid the preferred drug for most patients. Both options should be discussed with the patient (weekly oral vs. annual intravenous) and treatment chosen accordingly. Denosumab can be used as a first choice too if the patient reacts to or wants to avoid bisphosphonates. Teriparatide can be considered for some with very low BMD (T score <-3.5) and high risk of vertebral fracture.
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- Approved agents with efficacy to reduce hip, non-vertebral, and spine fractures include alendronate, risedronate, zoledronic acid, and denosumab, and these are appropriate as initial therapy for most patients at risk of fracture. Often oral bisphosphonates are preferred in low and moderate risk cases.

Recommendations for the management of osteoporosis in chronic kidney disease (CKD) patients and those on dialysis
- Management of patients with osteoporosis and CKD is difficult as bisphosphonates are contraindicated in stage 4 and 5 kidney disease (eGFR below 30 to 35 ml/min). Denosumab is not cleared by the kidney and therefore can be used in these patients. However, the risk of hypocalcemia is high with this agent, especially in patients in stage 5 disease. Optimal calcium intake and vitamin D status should be assured before starting denosumab.
- A major concern with antiresorptive therapy in patients with CKD is adynamic bone disease and selected patients should undergo undecalcified iliac bone biopsy if facilities are available, to guide correct decision making for the management of osteoporosis.

Rationale and Evidence

The multicentered prospective study from North India[700] followed up 264 patients for 12 months and found that ageing, osteoporosis, and diabetes are predictors of poor outcomes. We recommend development of newer strategies that target male as well as female patients with osteoporosis with particular attention to preventing in-house falls and fractures.

Background

Osteoporosis is a skeletal disorder characterized by diminished bone strength that increases the risk of fracture in instances of trivial trauma. Asians have a lower bone mass than the west [701,702]

Recent data suggest that type 1 and type 2 diabetes mellitus are significant risk factor for fractures. BMD tends to be low in patients with type 1 DM, BMD may be normal in patients with Type 2 DM and yet the fracture risk is increased, reflecting poor bone quality in these patients.[703] It is not known whether better control of DM mitigates the increased fracture risk.

Implementation
- Screening women above 40 in the absence of any high-risk factors [704]
- Screening for Vitamin D deficiency

Risk Factors

The following are the most common risk factors that can raise bone complications in diabetics [705]

1. Gender: Women had significantly lower BMD as compared to men
2. Vitamin D deficiency
3. Previous fragility fracture
4. Hypertension (controversial)
5. Diabetes
6. Cardiorespiratory illness
7. Rheumatoid arthritis (RA)
8. Smoking and alcohol
9. Sun exposure
10. Anemia
11. Renal dysfunction

Diagnosis

Clinical

Any adult with a fragility fracture should be suspected of having underlying osteoporosis (primary vs. secondary). In addition, historical height loss of more than 4 cm in postmenopausal women raises the possibility of asymptomatic vertebral fractures. Individuals with persistent back pain may have underlying vertebral fractures as well.

Dual-Energy X-ray Absorptiometry (DXA)

Dual energy X-ray absorptiometry, or DXA, is the most commonly used technique for measuring BMD. Although true density measurement is 3-dimensional, DXA is a two-dimensional measurement and thus calculates areal bone density.

BMD values are calculated in grams per cm^2 (or area of bone density). In order to account for differences across DXA equipment across different manufacturers, the values are further expressed in standard deviations (SD) units from the mean BMD value of the reference population
- 'T' score of an individual is the number of SD his/her BMD deviates from the mean BMD of 20-29-year-old reference population (usually Caucasian women- see further discussion below).
- 'Z' score of an individual is the number of SD his/her BMD deviates from the mean BMD of the same age, gender, and ethnic group reference population.

Indications for DXA measurement
- Women aged 60 and older and men aged 65 and older, regardless of clinical risk factors
- Postmenopausal women younger than 60 years and men aged 50-64 years when there are concerns for osteoporosis based on their clinical risk factor profile
- Women in the menopausal transition if there is a specific risk factor associated with increased fracture risk, such as low body weight, prior low-trauma fracture, or high-risk medication
- Individuals who have had a fragility fracture before the age of 50 years
- Individuals with a condition (e.g., rheumatoid arthritis, diabetes mellitus, malabsorption syndrome) or who are taking medication (e.g., glucocorticoids in a daily dose ≥5 mg prednisone or equivalent for ≥ three months) associated with low bone mass or bone loss
- Any individual being considered for pharmacologic therapy for osteoporosis

Biochemical investigations

Biochemical investigations should be directed at identifying the underlying cause of osteoporosis. In patients with osteoporosis, prior to initiation of pharmacotherapy, a basic biochemical and hormonal profile that includes serum calcium, phosphorous, total alkaline phosphatase, creatinine, 25-hydroxyvitamin D, and intact parathyroid hormone (iPTH) would be desirable. In patients with secondary osteoporosis, detailed blood investigations should be pursued based on clinical suspicion.

Bone turnover markers(BTMs)

BTMs are dynamic parameters that reflect short-term, acute changes in bone remodeling status that are not measured by BMD and are complementary to BMD measurement. However, BTMs have no role in the diagnosis of osteoporosis. Although BTMs are not routinely used to diagnose osteoporosis, they are increasingly used in the follow-up of patients who are on anti-osteoporotic treatments. Hence, wherever available, patients contemplating anti-osteoporotic therapy can get a baseline BTM level estimated prior to initiation of therapy for subsequent comparison during follow-up.

Follow up

Treatment of osteoporosis with either anti-resorptive or osteoanabolic therapy reduces the risk of incident fractures along with a subsequent reduction in morbidity and mortality. In a study assessing treatment algorithms in patients with osteoporosis in India, most clinicians preferred bisphosphonates as the first-line of therapy. However, in another study that aimed explicitly to evaluate the treatment adherence and compliance of postmenopausal osteoporotic women for different regimens of bisphosphonates in Indian postmenopausal women, the authors found that an adherence rate of 56% was found with the monthly regimens, 36% for weekly regimens, and 32% for daily regimens . Herein lies the paramount importance of continuous monitoring and vigilant follow-up.

Frequency of follow-up

- There exists no consensus regarding the frequency of follow-up for patients on anti-osteoporotic therapy. The first follow-up can be planned after 3 months following initiation of therapy. Thereafter, patients can be followed-up at 3-6 monthly intervals for 2-3 subsequent contacts followed by annual visits . This promotes adequate adherence to the treatment regime and reinforcement of fall prevention practices.

Clinical follow-up

- History

At each visit, a brief history with an emphasis on assessing new incident fractures, new-onset/worsening of kyphosis/scoliosis, new-onset or worsening of back pain, and perceptible height loss should be elicited. A history of falls is a predictor of future falls and hence should be specifically queried. Patients should also be asked about the possible side effects of anti-osteoporotic therapy, notably, thigh and jaw pain. At each and every visit, the need for continuation of treatment and regular follow-ups should be reinforced and family members/caregivers should be actively involved in decision making.

Physical evaluation

- A short physical examination focusing on the patient's height should be undertaken. Other characteristics to assess include spinal tenderness, kyphosis, decreased spacing between lower ribs and pelvis, and oral hygiene. Patients on anti-resorptive therapy with poor dentition may be referred to a dental physician for a detailed oral evaluation.

Drug holiday

- The concept of a "drug holiday" has been proposed to potentially reduce the incidence of the rare adverse events associated with long-term anti-resorptive therapy. However, the recommendation for drug holidays is still a matter of debate, especially since there is a dearth of data from India. A drug holiday can be considered in low-moderate risk patients following a course of bisphosphonate with fracture risk being revaluated every 1-3 year. There is no consensus on using BTMs to assess the need for drug holiday.
- Fall prevention is an integral part of comprehensive osteoporosis care, and physicians following up patients with osteoporosis should educate patients about fall prevention. Important points that need to be reiterated at each visit include use of low-heeled shoes with rubber soles for more solid footing, avoiding walking on slippery floors/sidewalks, using hand rails while walking up or downstairs, keeping rooms, bathrooms and stairs well lit, securing in-room carpets, and installing grab bars on the bathroom's walls.
- Thus, patients with osteoporosis on treatment require close monitoring and vigilant follow-up. A clinical assessment at 3-6 monthly intervals for the initial 2-3 visits and thereafter annually would be feasible in our setting. Wherever facilities are available, a DXA scan should be repeated every 2 years. If available, BTMs can be performed at least twice, at 3 months and 6 months following therapy initiation, and should ideally be compared with baseline pre-treatment values to assess patient compliance. Fracture risk should be evaluated periodically in patients on anti-resorptive therapy, and a drug holiday can be considered in patients with low-moderate risk of fracture.

Conclusion

Osteoporosis is a major public problem in India. However, diagnosing and effectively managing osteoporosis is challenging in the Indian setting. Since data indicates that osteoporotic fractures occur at an earlier age in Indians than in the West, screening for osteoporosis should begin at an earlier age. Maintaining optimum serum 25-hydroxyvitamin D levels is essential, which, in most cases would require regular vitamin D supplementation. Pharmacotherapy should be guided by the presence/absence of vertebral/hip fractures or the severity of risk based on clinical factors, although bisphosphonates remain the first choice in most cases. Regular follow-up is essential to ensure adherence and response to therapy.

SKIN

Different skin disorders in diabetes

- *Acanthosis nigricans:* This condition typically affects people who are obese and is a marker of insulin resistance. It sometimes goes away when a person loses weight.
- *Diabetic dermopathy:* Also known as "shin spots," the hallmark of diabetic dermopathy is light brown, scaly patches of skin, often occurring on the shins. These patches may be oval or circular. They're caused by damage to the small blood vessels that supply the tissues with nutrition and oxygen. This skin problem is harmless and doesn't require treatment. However, it often doesn't go away, even when blood glucose is controlled.
- *Fungal infections* The culprit in fungal infections of people with diabetes is often Candida albicans. This yeast-like fungus can create itchy rashes of moist, red areas surrounded by tiny blisters and scales. These infections often occur in warm, moist folds of the skin. Problem areas are under the breasts, around the nails, between fingers and toes, in the corners of the mouth, under the foreskin (in uncircumcised men), and in the armpits and groin. Common fungal infections include jock itch, athlete's foot, ringworm (a ring-shaped itchy patch), and vaginal infection that causes itching.
- *Localized itching* is often caused by diabetes. It can be caused by a yeast infection, dry skin, or poor circulation. When poor circulation is the cause of itching, the itchiest areas may be the lower parts of the legs.
- *Necrobiosis lipoidica diabeticorum:* Light brown, oval, and circular patches are also a hallmark of necrobiosis lipoidica diabeticorum (NLD). This condition is rarer than diabetic dermopathy. In the case of NLD, though, the patches are often larger in size and fewer in number. Over time, NLD skin patches may appear shiny with a red or violet border. They're usually itchy and painful. As long as the sores don't open, no treatment is required. It affects adult women more often than men, and also tends to occur on the legs.
- *Allergic reactions and Diabetic blisters (bullosis diabeticorum*)**:** Although rare, people who have type 2 diabetes and nerve damage may also get blisters that look like burns. They usually heal in a few weeks and aren't painful.
- *Eruptive xanthomatosis and Digital sclerosis:* This skin condition causes the skin on the hands, fingers, and toes to become thick, tight, waxy, and potentially stiff in the joints. Elevated blood sugar can increase the risk of developing digital sclerosis. Lotions, moisturizers, and regulated blood sugar levels can help prevent or treat the condition.
- *Disseminated granuloma annulare:* Disseminated granuloma annulare (disseminated GA) appears as red or skin-colored raised bumps that look like rashes, commonly on the hands or feet. These bumps may be itchy. They're harmless, and medications are available for treatment.
- *Acquired perforating disorders:* They are caused by local trauma, rubbing or due to deposition of hydroxyapatite leading to inflammatory reaction .The usual presentation is keratotic papules on extensor surface that are pruritic and may have follicular base with central plug. The retinoic acids, topical glucocorticoids and PUVA therapy is useful in treating these cases.

ADA Recommendation for Skin Care

- Keep good glycemic control. People with high glucose levels tend to have dry skin and less ability to fend off harmful bacteria. Both conditions increase the risk of infection.
- Keep skin clean and dry.
- Avoid very hot baths and showers. If your skin is dry, don't use bubble baths. Moisturizing soaps may help. Afterward, use a standard skin

lotion, but don't put lotions between toes. The extra moisture there can encourage fungus to grow.
- Prevent dry skin. Scratching dry or itchy skin can open it up and allow infection to set in. Moisturize your skin to prevent chapping, especially in cold or windy weather.
- Treat cuts right away. Wash minor cuts with soap and water. Only use an antibiotic cream or ointment if your doctor says it's okay. Cover minor cuts with sterile gauze. See a doctor right away if you get a major cut, burn, or infection.
- During cold, dry months, keep your home more humid. Bathe less during this weather, if possible.
- Use mild shampoos.
- Do not use feminine hygiene sprays.
- See a dermatologist (skin doctor) about skin problems if you are not able to solve them yourself.
- Take good care of your feet. Check them every day for sores and cuts. Wear broad, flat shoes that fit well. Check your shoes for foreign objects before putting them on.
- Talk to your doctor or dermatologist if you are not able to solve a skin problem yourself.

NON-ALCOHOLIC FATTY LIVER DISEASE

Recommendation

- All patients with T2DM and prediabetes be evaluated for NAFLD. They recommend evaluation for NAFLD by measuring baseline and yearly liver enzymes and referral to a specialized center for persistently elevated or worsening transaminases.
- The AASLD guidelines state that "there should be a high index of suspicion for NAFLD and NASH in patients with T2DM.They recommend the use of noninvasive measures of fibrosis, such as the NAFLD fibrosis score, fibrosis-4 index (FIB-4), or vibration-controlled transient elastography (VCTE) to identify those at low or high risk for advanced fibrosis.
- However, there is no clear consensus about how to implement screening and which patients should be referred to specialized centers.
- Patients with a FIB-4 score ≥1.3 should undergo further evaluation by a liver specialist.

Background

Type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD) commonly exist together and more precisely in Asian Indians. They both are consequences or a complication of metabolic syndrome. The presentations of NAFLD ranges from simple steatosis (NAFL) to non alcoholic steatohepatitis (NASH), and cirrhosis. NAFLD is defined or could be diagnosed as hepatic steatosis diagnosed either by histology/imaging with macrovesicular steatosis in >5% of hepatocytes according to histological analysis or by proton density fat fraction or >5.6% as assessed by proton magnetic resonance spectroscopy (MRS) or quantitative fat/water selective magnetic resonance imaging (MRI) with no secondary cause for steatosis. overall prevalence of NAFLD in T2DM Indian population was found to be 56.5%, which is in line with prevalence of 54.5% described by Mohan et al,10 but higher than the prevalence rate of 12.5% and 20.9% described in other studies. The corelation In Asian Indians could be predominantly due to presence of excess abdominal fat (abdominal subcutaneous and intra-abdominal fat) and lifestyle factors (imbalanced diets and physical inactivity), and presence of high grade insulin resistance.
- Data on drug management needs to be updated. SGLT2i data from India is important, as is GLP1RA data.
- Greater use of fibroscan has to be emphasized- ultrasound serves little purpose.

Risk Factors

- Type 2 diabetes mellitus
- Metabolic syndrome
- Obesity
- Physical inactivity
- Obstructive sleep apnea (important)

Screening

1. Incorporation of the FIB-4 score into the care checklist and care pathway to identify patients at high risk of NASH with advanced fibrosis.
- Addition of a platelet count and FIB-4 calculator to the care checklist of the patient with diabetes or prediabetes.The formula for FIB-4 is readily available online.
- Involvement of a patient navigator to

- flag patients who need laboratory measurements for the calculation of FIB-4;
- identify patients with indeterminate or high-risk FIB-4 scores who need referral to a specialized liver center and/or referral for VCTE;
- follow-up to ensure that the patient underwent VCTE or the specialist appointment.

2. Referral for VCTE
- FIB-4 <1.3: Low risk patients (patients are unlikely to have advanced fibrosis). Follow-up with PCPs for appropriate preventive interventions of lifestyle changes and a yearly calculation of FIB-4.
- FIB-4 ≥1.3: Refer the patient for VCTE

(i) if liver stiffness measure is <8 kPa: follow up with PCP and repeat FIB-4 and VCTE in 1 year; (ii) if liver stiffness measure is ≥8 kPa: Refer the patient to a liver specialist.

(Note, in case of VCTE failure, an alternative, such as shear wave elastography/acoustic radiation force imaging, magnetic resonance elastography [particularly when body mass index is >35 kg/m2] may be considered according to local availability).

3. Referral to specialized liver centers for further assessment of all patients with FIB-4 ≥1.3 and VCTE ≥8 kPa.

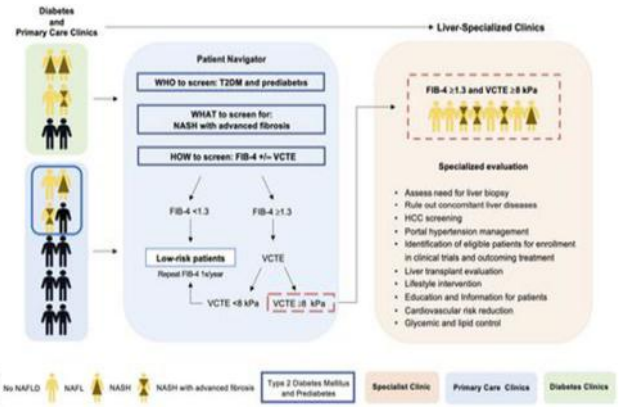


Figure 14: Screening algorithm for different populations

Complications

Among macrovascular complications mainly CVD in NAFLD is increased by 1.87-fold in the presence of T2DM. NAFLD has been associated with increased carotid intima-media thickness, increased coronary artery calcium score, early left ventricular diastolic dysfunction, decreased myocardial perfusion, and reduced myocardial high-energy phosphate metabolism in patients with T2DM.

NAFLD is also known to increase microvascular complications of diabetes such as chronic kidney disease and retinopathy.

A strong association between NAFLD and chronic kidney disease has been largely described in the literature.[706] NASH is associated with a 2-fold increase risk of chronic kidney disease, and patients with advanced liver fibrosis are at a 5-fold higher risk of chronic kidney disease compared to patients without fibrosis, independently of the presence of diabetes

Diagnosis

For high specific and sensitive diagnosis of NAFLD liver biopsy is the investigation of choice.

A non-invasive imaging test for steatosis is ultrasound (USG) (preferred for first-line diagnosis which shows increased echogenicity)
MRI and proton MRS or quantitative fat/water-selective MRI/fibroscan/ CT could be assessed as more sensitive diagnostic technique.

Rationale and Evidence
There have been studies done around the prevalence of clinically relevant liver fibrosis due to non-alcoholic fatty liver disease in Indian individuals with type 2 diabetes[707], low skeletal muscle mass is associated with liver fibrosis in individuals with type 2 diabetes and non-alcoholic fatty liver disease. [708]

Randomised Controlled Trials from India:
Effect of dulaglutide on liver fat in patients with type 2 diabetes and NAFLD: randomised controlled trial (D-LIFT trial)[709]: This trial concluded that when included in the standard treatment for type 2 diabetes, dulaglutide significantly reduces LFC and improves GGT levels in participants with NAFLD. There were non-significant reductions in PFC, liver stiffness, serum AST and serum ALT levels. Dulaglutide could be considered for the early treatment of NAFLD in patients with type 2 diabetes.

Effect of Empagliflozin on Liver Fat in Patients With Type 2 Diabetes and Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial (E-LIFT Trial)[710]: This trial concluded that when included in the standard treatment for type 2 diabetes, empagliflozin reduces liver fat and improves ALT levels in patients with type 2 diabetes and NAFLD.

Dapagliflozin Improves Body Fat Patterning, and Hepatic and Pancreatic Fat in Patients With Type 2 Diabetes in North India[711]:
Trial concluded that Dapagliflozin, after 120 days of use, reduced pancreatic and liver fat and increased insulin sensitivity in Asian Indian patients with T2DM.

Management
The interventions for the management of NAFLD should have an indirect effect which improves IR and glycemia as Insulin Resistance (IR) is considered a major pathophysiological mechanism behind NAFLD in Diabetes and thus are used for the treatment ofT2DM as well as for the treatment of NAFLD also pharmacotherapy has to be reserved for those with highest risk for disease progression in NAFLD. Definitive clinical trials are limited. NOTE - Some of the drugs such as ursodeoxycholic acids are not recommended for the treatment of NASH/NAFLD

Statins
Many patients with T2DM are treated with statins to decrease risk of CVD, and in 2006 the Liver Expert Panel stated that statins can be safely used for dyslipidemia in patients with NAFLD/NASH Statins can be used in dyslipidaemia with increased baseline liver enzymes. But however until more randomized clinical trials prove their efficacy, statins should not be used to specifically treat NAFLD/NASH.
The GREACE trial also showed the safety of statins in NAFLD/NASH. Although use of statins in NASH cirrhosis is safe but it should be avoided in decompensated cirrhosis.

Omega-3 Polyunsaturated Fatty Acid
Hypertriglyceridemia or high TG, which often coexists in NAFLD and T2DM, can be treated with high-dose omega-3 polyunsaturated fatty acid (PUFAs) but their use to specifically target fatty liver is still uncertain. More detailed real world evidences are required.

Vitamin E
Oxidative stress occurs in both NAFLD and T2DM which is a predictive precursor for macro as well as microvascular complications. According to PIVENS trial, 800 IU/day of Vitamin E for 96 weeks improved liver enzymes, steatosis, inflammation, and ballooning (except fibrosis) and induced resolution of NASH in 42% of patients.

Metformin
Metformin is considered as the first-line therapeutic agent for the treatment of T2DM. Metformin decreases body fat with an improvement in hepatic insulin sensitivity. But for the treatment of NAFLD without diabetes, there is no license or proper recommendation for the use of metformin. But it has been seen that there is an improved survival in cirrhosis and HCC even though definitive improvement in steatosis or histological features of NASH has not been established.

Thiazolidinediones
Pioglitazone cause adipose tissue sensitization to insulin through activation of PPARϒ resulting in fatty acid uptake and storage. There is also an increase in adiponectin with amelioration of pro-inflammatory adipokines, thus reducing gluconeogenesis and fatty acid influx improving insulin sensitivity. They also cause restoration of normal adipose tissue biology and result in an improvement in hepatic steatosis. PIVENS trial compared low-dose pioglitazone versus Vitamin E versus placebo for 2 years in patients without overt diabetes and concluded that pioglitazone (improved all histological features [except for fibrosis]) and resolution of NASH was achieved more than placebo. Cusi et al. in a double-blind randomized placebo-controlled study concluded that there was reduction in hepatic steatosis, inflammation, and ballooning without worsening of fibrosis with pioglitazone in NASH with prediabetes or T2DM. Improvement in fibrosis, insulin sensitivity in liver, skeletal muscle, and adipose tissue was also present and the positive outcomes were maintained even after 36 months of treatment.

Glucagon-Like Peptide-1 Analogs
But definitive data needs to be explored.Glucagon-like peptide-1 (GLP-1) analogs by its weight loss of GLP-1 receptor as seen in animal studies. property can result in an improved hepatic steatosis and steatohepatitis and also by the expression

Insulin secretagogues: sulfonylureas
They stimulate insulin secretion and are associated with a higher risk of severe hypoglycemia than metformin and other drugs in patients with advanced age and chronic liver or kidney disease. They do not modify IR neither any improvement is seen with perspective to NAFLD, their use is not recommended specifically for NAFLD.
Glibenclamide (glyburide) and gliclazide are metabolized in the liver and eliminated through bile and kidney. Hepatotoxicity has been reported with glibenclamide and gliclazide. Therefore their use is not recommended in NAFLD or hepatic impairment.

Meglitinides
Repaglinide and Nateglinide are the 2 most commonly used drugs. They stimulate the beta cells of the pancreas, both agents are metabolized in the liver, however, repaglinide is rapidly eliminated through the bile and its rate of elimination is significantly reduced in patients with CLD thus, it may induce hypoglycemia and it is contraindicated in patients with advanced liver insufficiency but its use in NAFLD grade I and II could be indicated. In contrast, the pharmacodynamics of Nateglinide is not altered in patients with CLD and is considered to be safer.

SGLT 2 I
SGLT2 inhibitors reduce plasma glucose levels by inducing glucosuria and osmotic diuresis. They should be carefully administered to patients with risks of hypovolemia (older age, cardiovascular diseases, treatment with diuretics, liver cirrhosis with circulatory dysfunction). They are contraindicated in patients with renal impairment grade IV or eGFR less than 30 mg/dl. Their use in NAFLD has not been established out clear as in direct or indirect effect. But should be avoided with higher risk of hypovolemia.

Glitazars
Saroglitazar is a glitazar class compound that has been approved by the central drug standard control organization of India for treating diabetes

dyslipidemia with the excellent safety profile. Real-world evidence has showed that there was also a consistent improvement in liver parameters with reduction in ALT levels in NAFLD. Studies in northern India have shown improvement in liver parameters such as SGPT in diabetic dyslipidemia patients with NAFLD who received saroglitazar.

Bariatric Surgery

Indication for bariatric surgery is noncirrhotic NASH unresponsive to lifestyle changes and pharmacotherapy. Clearance of NASH was seen in 85% of patients, and inflammation and fibrosis in 37% and 20%, respectively. This was actually attributed to weight loss. The prevalence of metabolic syndrome reduced from 70% to 14%, i.e., there was a resolution of hypertension, dysglycemia, and dyslipidemia in 85%, 93.8%, and 95.6% of patients, respectively. Portal hypertension should be excluded before attempting surgery.

OBESITY AND TYPE 2 DIABETES MELLITUS

Recommended Care

- The cut-off points for overweight and obesity in Indian patients with T2DM patients are as follows:
  - BMI 18-22.9 kg/m^2: Normal
  - BMI 23-24.9 kg/m^2: overweight
  - BMI ≥25kg/m^2: Generalized obesity
    Waist circumference (WC) ≥90 cm for men and ≥80 cm for women: abdominal obesity
- Criteria for metabolic syndrome are as follows:
  - Abdominal or central obesity (WC ≥90 cm for men and ≥80 cm for women) plus
  - Any 2 of the following four factors:
    - » Increased triglycerides (≥150 mg/dL or specific treatment)
    - » Reduced HDL cholesterol (men: <40 mg/dL; Women: <50 mg/dL or specific treatment)
    - » Increased blood pressure (systolic BP ≥130 or diastolic BP ≥85 mm Hg or treatment of previously diagnosed hypertension)
    - » Increased fasting plasma glucose (FPG ≥100 mg/dL or previously diagnosed T2DM)

Management Strategies:

- Maintaining a healthy lifestyle is recommended for the management of the metabolic syndrome
- Moderate calorie restriction (to achieve a 5%-10% loss in body weight)
- At least 150 mins/week of physical activity is recommended, which includes aerobic exercise, work-related activity, and muscle strengthening activity. It is to be increased to 300 mins/week.
- Change in dietary composition (low-calorie diet)
- Combination of aerobic and resistance training exercise
- Change in behavioral pattern
- Pharmacotherapy for obese patients with T2DM should be considered in addition to lifestyle changes in those with BMI ≥25 kg/m^2
  - GLP-1 analogs and SGLT2 inhibitors should be preferred as add-ons to metformin in obese patients with T2DM
  - Lipase inhibitors (orlistat) may be used for inducing weight loss in addition to OADs in patients who have BMI >25 kg/m^2
- Surgical treatment (bariatric surgery) may be considered an option in patients with T2DM with BMI >32.5 kg/m^2 who cannot achieve sustainable weight loss and improvement in the severity of co-morbidities, including hyperglycemia, despite proper nonsurgical management.
- Surgical options for weight loss surgery include:
  - Restrictive procedures: Laparoscopic adjustable gastric banding (LAGB) and sleeve gastrectomy. Gastric balloons/other devices may be tried if surgery cannot be done.
  - Malabsorptive procedures: Biliopancreatic diversions (BPD)
  - Combined procedures: Roux-en-Y gastric bypass (RYGB)
  - Experimental procedures: Ileal interposition and duodenojejunal bypass, various implantable pulse generator
- Comprehensive lifestyle changes including dietary modification, exercise, behavioral management and pharmacotherapy, and bariatric surgery in select patients are the most effective interventions for weight management in T2DM patients

Background

Obesity is a highly prevalent metabolic disorder that is often associated with T2DM.[712,713] For adults, WHO define overweight as BMI of ≥25 kg/m^2 and obesity as BMI of ≥30 kg/m^2.[714] However, WHO and International Obesity Task Force (IOTF) suggested BMI cut-offs of 23 and 25 kg/m^2 for Asian Indian adults for overweight and obesity, respectively.[715,716] Furthermore, the World Health Organization Asia Pacific Guidelines defined generalized obesity (GO, BMI ≥25 kg/m^2), abdominal obesity (AO, WC ≥90 cm for men and ≥80cm for women), and combined obesity (CO = GO plus AO) for Asian population.[715–717] In India, the prevalence of obesity is rising at an alarming rate, primarily affecting the urban population.[712,718] The ICMR-INDIAB study data reports that about 135, 153, and 107 million individuals in India might suffer from GO, AO, and CO, respectively, if extrapolated to the whole country.[717–719] Furthermore, female gender, hypertension, diabetes, higher socioeconomic status, physical inactivity, and urban residence were significantly associated with obesity in the Indian population. Indians have an increased predisposition to diabetes attributed to the "Asian Indian Phenotype" characterized by lesser GO measured by BMI and more significant central body obesity. More truncal fat, as shown by greater WC and WHR.[712,720–724] Abdominal obesity contributes significantly to metabolic alterations such as Insulin Resistance (IR), dysglycemia, and dyslipidemia.[718,724–728] T2DM is closely linked to obesity, particularly adult weight gain, and is the main contributor to rising healthcare costs. While it seldom develops with BMI <21 kg/m^2, most people with T2DM have a BMI >25 kg/m^2, and around 50% have a BMI >30 kg/m^2.[729]

High consumption of sugars among children and adults in India may also have clinical significance, given the increased tendency for Indians to develop IR, abdominal adiposity, hepatic steatosis, and the increasing "epidemic" of T2DM.[712,730] Because Asian Indians tend to develop diabetes at a significantly lower BMI and WC than white Europeans, lower thresholds of BMI to define overweight (BMI: 23-24.9 kg/m^2) and obesity (BMI ≥25 kg/m^2) were proposed by IDF and National Institute of Health and Care Excellence (NICE).[731,732]

Considering the increasing prevalence of obesity in both developed and developing countries and a higher risk for developing IR, dyslipidemia, dysglycemia, and a higher Cardiovascular risk at lower levels of BMI in Indians, a consensus meeting was convened in New Delhi in 2008[733] to redefine the cut-offs for BMI and WC.

Diagnosis of Obesity and Abdominal Obesity:

For diagnosing overweight and obesity in the Indian population, according to this consensus statement, a BMI of 18–22.9 kg/m^2 should be considered normal, a BMI of 23–24.9 kg/m^2 should be regarded as overweight, and a BMI ≥25 kg/m^2 indicates the presence of obesity. The upper limit for WC for men and women was defined as 90 cm and 80 cm, respectively.[718]

Normal Weight Obesity and Diabetes in India

Those who are not obese by the current criteria may have higher body fat and excess fat in the ectopic sites.[734,735]In a recent study from Kerala; it was found that about a third of the study population (n=1147) had higher body fat percentage despite having a BMI in the non-obese category. The prevalence of diabetes, hypertension, and dyslipidemia is similar in these individuals with normal weight obesity compared to those with overt obesity in the Indian population.[736] Moreover, this phenotype is more resistant to lifestyle intervention in the Indian setting. However, more data are needed.[737]

COVID-19 and Obesity

The COVID-19 pandemic has severely influenced the world's lifestyle, with no exception for the diabetic population. Weight gain due to a disturbed lifestyle has been seen during the COVID-19 epidemic. The presence of obesity itself is a substantial risk factor for severe COVID-19 and mortality[738] and this could be further aggravated due to diabetes.[739]

Sarcopenic Obesity

Sarcopenia is a decreased muscle strength, function, and mass predominantly due to age. Sarcopenic obesity is applied when sarcopenia is combined with excess body fat. Multiple factors are responsible for sarcopenic obesity, such as lack of physical activity, malnutrition, low-grade inflammation, and insulin resistance. It is related to excess morbidities, mortality, and delayed recovery from any acute condition. Hence, sarcopenic obesity demands identification and intervention at an early stage. Criteria from a recent Indian study (Sarco-Cubes study) could be followed for the diagnosis of sarcopenia, and BMI>25 kg/m^2 should be taken for diagnosis of obesity.[740]

Obesity, Type 2 Diabetes, and Increased Risk of Cancer

Individuals with obesity and T2DM are at a greater risk of developing multiple cancers, including breast, prostate, colorectal, gastric, pancreatic, and hepatic.[741] Multiple potential metabolic abnormalities in obesity and T2DM may explain the increased risk of cancer and cancer-related mortality in these patients.[742–744]

Clinical Considerations

The following factors were considered when framing recommendations for obesity that were reviewed in the Indian context: high prevalence of obesity, high abdominal adiposity, increased fasting insulin and IR, nutritional factors, atherogenic lipid profile (increased triglycerides and LDL and low HDL).[733]

Identification of obesity in patients with type 2 diabetes

- At first and on each subsequent visit, patients with T2DM should be screened for the presence of excess body weight using appropriate anthropometric measurements (BMI and WC). They should be classified as overweight or obese based on cut-off values recommended for the Indian population.
- Based on the current evidence, WC is preferred over WHR as a measure of abdominal obesity with Asian Indian specific cut-offs.[733] Asian Indians have higher morbidity at lower cut-offs for WC than the western population; ≥90 cm in men and ≥80 cm in women.[726,733] Measurement of waist circumference should be done by standard method.[745]

Lifestyle interventions

- Lifestyle interventions, including diet therapy, physical activity, and behavioral and psychosocial strategies, have shown positive health outcomes in obese patients with T2DM patients. The Diabetes Prevention Program (DPP)[746] and the Look AHEAD (Action for Health in Diabetes) trial[747] report clinically significant weight losses averaging 4-5% (or 4–5 kg) at 3–4 years with lifestyle intervention. Similarly, an RCT including Asian Indians reported that subjects with less education lost a model-predicted 3.30 kg more in weight and 4.95 cm more in WC than those with more formal education.[748]
- The lifestyle interventions for overweight or obese T2DM patients should be based on decreased energy intake and increased energy expenditure to produce a negative energy balance. This includes a low-calorie diet with a higher fiber intake, lower intake of saturated fats, optimal ratio of essential fatty acids, reduction in trans fatty acids, slightly higher protein intake, lower intake of salt, and restricted sugar intake.[749] High-protein meal replacement diet-based intervention in overweight/obese Asian Indians has shown a significant reduction in weight, abdominal obesity, blood pressure, lipids, glycemic parameters, and hepatic enzymes compared with a standard control diet in Indians.[750] Although studies assessing the ideal carbohydrate intake for people with diabetes are inconclusive, modifying carbohydrate intake considering the blood glucose response is of value, especially in the Indian context, where carbohydrate intake across all regions of India is very high.
- Behavioral therapy should address modifiable factors such as eating patterns and exercise habits that can significantly impact the management of obesity. A review of the Indian scenario suggested that slow eating techniques and stimulus control (not being distracted by television, books, or other materials) positively affect weight loss.[751] In obese patients with T2DM patients, IDF recommends not only moderate calorie restriction but also a moderate increase in physical activity as a part of behavioral therapy to promote weight loss (5–10% loss of body weight in the first year).[752] Other essential components of behavioral therapy embrace self-monitoring, goal setting, and stimulus or cue control. Such strategies help set realistic goals, guide patients in identifying stimuli that lead to excessive nutrient intake, and eliminate them accordingly.[753]
- Body weight is inversely associated with physical activity.[754] Patients with low physical activity have a 3-fold greater risk of significant weight gain in men and almost a 4-fold in women.[755,756] This association was stronger for women than men and the obese compared to average weight or overweight individuals.[757] Furthermore, prolonged exercise is associated with improved metabolism and muscle mass conservation during dietary restriction.[758,759] An RCT comprising 262 sedentary men and women reported that a combination of aerobic and resistance training exercise reduced WC from −1.9 to −2.8 cm and mean fat mass of −1.7 (−2.3 to −1.1 kg; p<0.05) compared with the non-exercise group.[760] Physical activity, including aerobic, work-related, and muscle strengthening, should be prescribed at the individual, community, and societal levels to help Asian Indians become more physically active (Table 1). As per the WHO recommended levels of physical activity for adults (18-64 years), it should be at least 150 minutes of moderate-intensity weekly or 75 minutes of vigorous-intensity aerobic physical exercise weekly.[761]
- In the Diabetes REmission Clinical Trial (DiRECT), 306 patients with T2DM, with a BMI of 27-45 kg/m^2 and not receiving insulin, were assessed for the remission of T2DM during a primary care-led intensive weight management program. At 12 months, almost half of the participants, 68/149 (46%), achieved remission versus 4% in the control group to a non-diabetic state and were off antidiabetic drugs. At 24 months, 64% of those who had lost more than 10 kg were still in remission.[762,763]
- The randomized controlled PREVIEW lifestyle intervention study reported that total physical activity accounts for more significant variance in IR and some related cardiometabolic risk factors than moderate-to-vigorous physical activity. In adults with prediabetes, objectively measured physical activity and sedentary time have been associated with cardiometabolic risk markers.[764,765] Fixed low-energy diet has been shown to induce an overall 11% weight loss and showed significant improvements in insulin resistance; men appeared to benefit more than women.[766]
- Short-term weight loss has also been seen with the Ketogenic diet and Intermittent fasting in obese patients. However, long-term data are not available. Specifically, more trials are needed in patients with T2DM. Therefore, prescribing aerobic and resistance training exercises in individuals with T2DM can improve metabolic control while reducing obesity and its related complications.
- Caloric restriction and increased protein intake to promote muscle growth based on individual characteristics. Treatment mainly revolves around dietary and physical activity interventions to reduce 5-10% of body weight. There is no recommended pharmacotherapy for sarcopenic obesity, but the same treatments for obese patients may be indicated.

Table 19: Physical activity prescription for aerobic and muscle strengthening exercise[733]

Type of physical activity	Moderate intensity modality	Duration	Frequency/ days per week	Vigorous intensity modality repetitions	Duration	Frequency / days per week
Aerobic physical	Brisk walking, stair	30 min	7	Football, badminton,	20 min	3
activity	climbing, jogging (4-7			basketball, running, rope		
	m/s), cycling, treadmill and swimming			jumping, dancing		
Muscle	Resistance weight training,	1-3 sets of 8-12	2-3	Resistance weight training,	>3 groups of >12	2-3
strengthening activity	curls, presses, anti-gravity exercise, isometric	repetitions targeting major		curls, presses, anti-gravity exercise, isometric	repetitions targeting major	
	exercise, children-body	muscle groups		exercise, children-body	muscle groups	
	weight activity (pull-ups)			weight activity (pull-ups)		

Pharmacotherapy

Though lifestyle modifications effectively induce weight loss and improve the diabetic status, they often fail. Initiation of pharmacotherapy is required quite often.

Metformin is the drug of the first choice for T2DM, with some evidence of weight loss.[767,768] Addition of acarbose may also produce a small amount of weight loss. Though these two drugs have a favorable effect on weight loss, they are not considered potent weight loss drugs. [59, 60, 61,62, 63, 64]

Available choices of weight loss options in patients with T2DM are as follows**:-**

Orlistat (tetrahydrolipstatin),

It is a lipase inhibitor and causes modest weight loss by blocking fat absorption from the gut. Combined with lifestyle changes, it was found to be effective in reducing weight and preventing diabetes.[721] A recent systematic review and meta-analysis report that treatment with orlistat and lifestyle intervention resulted in significantly more significant weight loss and improved glycemic control in overweight and obese T2DM patients compared with lifestyle intervention alone.[769]

Anti-hyperglycemic Drugs with Potential for Weight Loss

GLP-1 Receptor Agonists

GLP-1 Receptor Agonists (GLP1 RA) were approved for the first time in 2005 to treat diabetes. Since then, newer molecules from the class have been introduced, almost all injectable; Exenatide administered twice daily, Lixisenatide and Liraglutide once daily, Dulaglutide, Albiglutide, and Semaglutide once weekly. An oral GLP-1 RA, namely oral Semaglutide, is now available in India. In part, the weight loss effect of GLP-1 RAs is mediated by their appetite suppression effects. Additionally, they cause abdominal fullness and early satiety, thus reducing caloric intake[770]. Further, food choices toward less calorie-dense foods may be influenced by GLPI-RA [771].

Although most guidelines worldwide recommend using GLP1 RA in type 2 diabetes patients with a heightened risk of atherosclerotic vascular disease and diabetic kidney disease, the usage is not as expected, mainly owing to the high cost of therapy and gastrointestinal adverse effects. Besides, it is contraindicated in patients with a history of pancreatitis, diabetic retinopathy, and medullary thyroid cancer.

In general, higher doses of GLP-1 RA would be required for weight loss than those used for glycemic control. An up-titration of the amount is needed for optimal effects (Figure 1).

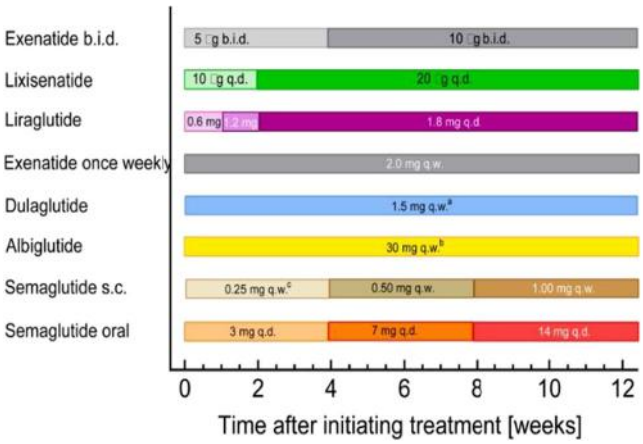
SGLT2 Inhibitors

SGLT2 inhibitors promote weight loss and provide cardiovascular and renal benefits. They cause a more significant loss of visceral fat mass than lean mass. In a double-blind RCT on patients with T2DM, SGLT2i, when added to patients uncontrolled with metformin, reduced body weight by 4.54 kg, waist circumference by 5.0 cm, and fat mass by 2.8 kg over 102 weeks[772]. In a retrospective analysis from India, T2DM patients who lost maximum weight were significantly younger; and had higher use of metformin, SGLT2i, and GLP1-RA[773]. Bays et al. showed that canagliflozin 100 mg reduces body weight by 2.8 kg in obese patients without diabetes[774]. A systematic review and meta-analysis of 6 RCTs involving 872 individuals on the use of SGLT2i in overweight or obese adults without diabetes found that, compared to the placebo group, the SGLT2i group had statistically significant reductions in body weight (1.42 kg vs. 1.14 kg; P<0.00001) and BMI (0.47 vs. 0.31; P<0.00001)[775]. [70.] In a recent Indian study, a statistically significant reduction in weight, BMI, body fat, circumferences, and all skinfold thickness was seen after 90 days of treatment with dapagliflozin. Still, handgrip strength increased, meaning betterment of skeletal muscle function.[776]

GLP-1RA and SGLT2i Co-administration

Co-administering SGLT2i with GLP1-RA in obese patients without diabetes reduces body weight by 4.5 kg at 24 weeks, and the weight loss was maintained for up to 1 year (5.7 kg)75. A combination of SGLT2i and GLP1-RA for weight loss is expected to provide a complimentary benefit, as SGLT2i causes weight loss by calorie loss and GLP1-RA promotes weight loss by decreasing calorie intake.

Figure 15: Recommendations for initial up-titration of GLP-1 RA[777]



Liraglutide in Children

The USFDA approved Liraglutide in 2019 for managing pediatric (at or above ten years of age) patients with T2DM following the landmark Ellipse trial[778]. In 2020, it was approved for chronic weight management among patients with obesity aged 12 years and older, as defined by age and gender-specific BMI cut-offs corresponding to an adult BMI of 30 kg/m^2 or higher.

Dual GIP/GLP-1 Receptor Agonist, Tirzepatide

It is the first dual GIP/GLP-1 agonist. It is a promising agent for the treatment of both diabetes and obesity. The most common side effects

of Tirzepatide are related to the gastrointestinal tract, like nausea, vomiting, and diarrhea [779]. The USFDA approves it for the treatment of diabetes. It is administered subcutaneously once a week. A systematic review and meta-analysis showed that all doses of Tirzepatide were superior to placebo, long-acting GLP-1 RAs, and basal insulin in reducing HbA1c and body weight [780]. Overall, it is one of the most potent drugs for weight loss. This drug is not yet available in India.

Metabolic Surgery

- The surgical options for weight loss include laparoscopic adjustable gastric banding (LAGB), sleeve gastrectomy, Roux-en-Y gastric bypass(RYGB), biliopancreatic diversion (BPD), ileal interposition and duodenojejunal bypass, and various implantable pulse generators.[733]
- Metabolic surgery is indicated in patients with BMI >32.5 kg/m^2 with co-morbidity or BMI >37.5 kg/m^2 without co-morbidity who fail to lose weight with medical management.[733] Several studies suggest that bariatric surgery provides durable glycemic control compared with intensive medical therapy.[781–784] Moreover, gastric bypass has been observed to uniquely restore the pancreatic β-cell function and reduce visceral fat, thus reversing the core defects in diabetes.[781] A systematic review and meta-analysis of RCTs report that RYGB surgery is superior to medical treatment for the remission of T2DM and improvement of the underlying metabolic defects and other CV risk factors.[785]
- Laparoscopic sleeve surgery and RYBG were safe and effective treatment options among the obese Indian population with T2DM, with significant remission rates of 77% and 85%, respectively (p<0.001), with substantial reductions in HbA1c and diabetes medication usage.[786–788]

Medical Devices for Weight loss and Weight Management

The FDA has recently approved several minimally invasive medical devices for short-term weight loss, which can be used for obesity management in T2DM patients.[789]

- At present, there are four types of FDA-regulated devices intended for weight loss:

- The gastric band can be placed around the top portion of the stomach, thereby leaving a small amount available for food
- Electrical stimulation systems block nerve activity between the brain and stomach using electrical stimulators which are placed in the abdomen
- Gastric balloon systems act by delaying gastric emptying using inflatable balloons placed in the stomach to utilize space.
- Gastric emptying systems drain food after eating with the help of a tube that is inserted between the stomach and outside of the abdomen.

Summary

- Treating obesity is an essential and often neglected aspect of diabetes treatment. The clinician should choose appropriate regimens to aid the patient in weight management and thus improve the quality of care.
- There is strong and consistent evidence that in obese or overweight patients with Type2 DM, weight management can improve glycemic control and reduce the amount of glucose-lowering medications[37-42]
- There is data to suggest that intense caloric restriction and 10-15 kg weight loss may lead to a lowering of HbA1c and, in some instances, remission of Type 2 DM for at least two years.[52]
- Several glucose-lowering medications, namely the SGLT2-I and GLP1 RA, afford weight reduction and other pleiotropic benefits in addition to glycemic management and should be an early consideration in an obese patient with Type 2 DM.
- Metabolic surgery has been associated with significant improvement of type 2 DM and other co-morbidities and reduced mortality.[77-81]

Table 20: Treatment for Overweight and Obesity in Patients with Type2 DM

Treatment Options	BMI≥23-24.9 kg/m^2	BMI ≥ 25-32.5 kg/m^2	BMI ≥32.5-37.4 kg/m^2	BMI≥37.5 kg/m^2
Diet and Lifestyle	*	*	*	*
Medications	*	*	*	*
Surgery			††	€€

*Indicate treatment initiation at indicated BMI cut-off

†† For select patients who fail to lose weight and have uncontrolled diabetes after at least one year of medical, behavioral, and lifestyle interventions

€€ For choose patients with morbid obesity can proceed directly to surgery after a detailed discussion with the patient and physician.

VACCINATIONS IN PEOPLE WITH DIABETES

Recommendations

Recommended Care

- All diabetes subjects should be educated about administering at least pneumococcal and influenza vaccines.
- Vaccination against pneumococcal disease, including pneumococcal pneumonia, with the 13-valent pneumococcal conjugate vaccine (PCV13) is recommended for children before the age of 2 years.
- People with diabetes aged 2 through 64 should receive a 23-valent pneumococcal polysaccharide vaccine (PPSV23). At age ≥65 years, regardless of vaccination history, additional PPSV23 vaccination is necessary.
- Annual vaccination against influenza is recommended for all people ≥6 months of age, especially those with diabetes.
  - Quadrivalent influenza vaccine should be preferred to bivalent.
- Vaccination is contraindicated/postponed in patients with:
  - Hypersensitivity to the active substances or any of the excipients of the vaccine
  - History of chicken egg allergy, particularly when considering a flu shot
  - Recent history of Guillain-Barre syndrome within six weeks of previous influenza vaccination in the case of a flu shot
  - Postponed in patients with febrile illness or any acute infection.
- Depending on the risk and need, other available vaccinations can be considered for diabetes.
  - Hepatitis
  - Herpes
  - HPV
  - COVID-19

Limited Care

The principles for infections and vaccinations with diabetes are recommended care subject to the availability and affordability of pneumococcal and influenza vaccines.

Background

The risk of developing infectious diseases due to diabetes is now considered a significant complication of diabetes.[790,791] Diabetes increases the risk of infection by two to three times compared to the non-diabetic population. The morbidity and mortality associated with infectious diseases such as influenza, pneumonia, and hepatitis, which is usually preventable by appropriate vaccination, also appear to be very high in diabetes subjects.[792] Patients with T2DM, especially those with PVD, are at increased risk for many typical and atypical infections due to immune dysfunction, DN, and poor circulation.[793] Furthermore, skin breakdown in patients with advanced diabetes and PVD provides a portal of entry for bacteria. Longer duration of diabetes and poor glycemic control causes an increased risk of pneumonia related hospitalizations in diabetes subjects due to the compromised immune system of the host.[794] A recent study demonstrated that patients with high blood glucose levels are at increased risk of community-acquired pneumonia.[795,796] Even certain viral infections can lead to new onset of diabetes in the population genetically prone to develop diabetes.

Considerations

The decision to conduct a screening program should be based on local factors such as limited resources and the high prevalence of diabetes-related infections that were reviewed in the Indian context.

Rationale and Evidence

Infections in diabetes

- Several factors have been implicated for infections in diabetes, of which altered immunity is the most predominant one.[793,797] Other predisposing factors increases susceptibility to infections include diabetes-related complications, frequent catheterization and dialysis in chronic renal failure patients. Evidence that these immunological defects can be corrected through reasonable glycemic control, supports the importance of close monitoring of infectious diseases in subjects with diabetes.[798]
- Urinary tract, respiratory tract, foot, and deep soft infections are most common in T2DM, with increased incidence and high mortality.[799,800]
- The following section deals with evidence from Indian and global studies on infections that commonly occur in patients with diabetes

  - Influenza: Diabetes increases the risk of hospitalization after influenza infection and quadruples the risk of intensive care unit (ICU) admission after hospitalization.[801] Death rates among patients with diabetes during influenza epidemics may increase up to 5–15%.[802] Evidence that influenza can trigger coronary complications, when taken in the context of diabetes subjects, gains more significance since the risk for CVD is already 2-to 4-fold higher in this subgroup.[800,803]
  - Infections of hand and upper limb: Diabetes ulcers in the upper limb should be promptly treated with adequate surgical means to prevent the spreading of infection. Creating awareness of healthy cleaning practices minimizes disability and results in a better outcome.[804]
  - Hepatitis: It has been observed that several patients with underlying diabetes suffer from a prolonged or complicated course of acute viral hepatitis. It is possible that with impaired hepatocyte regenerating capacity, these patients run a more prolonged and complicated course. In the diabetes population, hepatitis B and C produces more comorbidities and prolonged infections.

  - Even though the hepatitis B virus (HBV) itself may not cause diabetes directly, cirrhosis derived from HBV infection poses a two-fold higher risk for T2DM.[805] Infection due to HBV may occur during monitoring of blood glucose and other procedures involving multi-patient use of finger stick devices designed for single-patient use and inadequate disinfection and cleaning of blood glucose monitors between patients.[806]
  - When hepatitis C virus (HCV) infection occurs in diabetes patients, the chronicity and the risk of infections increase. A meta-analysis of 22 studies found that patients with T2DM were at higher risk for acquiring HCV than non-T2DM patients (OR: 53.50, 95% CI: 52.54, 54.82).[807]
  - Hepatitis A is the most common vaccine-preventable virus acquired during travel and is highly prevalent in the Indian subcontinent. Protection with hepatitis A vaccination is proven to last at least 15 years.[808]
- Data from a systematic review of 13 observational studies indicate that efforts to diagnose, detect, and treat diabetes early may have a beneficial impact on TB control.[809]

Types of vaccines

Various types of vaccinations recommended to prevent these infections are:

- Pneumococcal vaccination: Two pneumococcal vaccines are available: PPSV23 and PCV13. Secondary immune response after PCV13 immunization is higher, whereas the response is lower after immunization with the PPSV23 vaccine.[810]
- The panel recommends the use of PCV13 for adults ≥50 years followed by a dose of PPSV23 at least 1 year later (and at least 5 years after their previous PPSV23 dose) depending on the clinical judgment of the physician. These recommendations are in line with the guidelines from the ADA 2017 and are also in synergy with the guidelines released recently by the Indian Society of Nephrology 2016, Indian Academy of Allergy 2017, and the Geriatric Society of India 2015.[811–814]
- PCV13 is available for vaccination of older adults and must be considered an important step for vaccinating older diabetes patients with an age of >50 years. PPSV23 may be offered to immune-compromised patients with diabetes for additional coverage after PCV13. Repeated vaccination with PPSV23 must be avoided to prevent hypo-responsiveness. Clinical judgment in relation to individual subjects should be relied upon before these recommendations are put into practice.
- Influenza vaccination: In all patients with T2DM with age ≥6 months, excluding those allergic to eggs, influenza vaccine is recommended.[815,816] Influenza vaccination among diabetes patients reduced hospital admissions by 79% in two influenza epidemics in England.[817]
- HBV: To all unvaccinated patients with diabetes of 19–59 years, three-dose series of HBV is recommended.[816] In unvaccinated patients ≥ 60 years of age, the three-dose series vaccine could be considered.[816]
- Apart from the vaccines mentioned above, other routinely recommended, age-related vaccines should also be provided to all diabetes patients.[816]

Methods to improve the rate of vaccination

- Despite the importance of vaccination in diabetes patients, vaccination rates are low. In a survey on 307 diabetes patients in Singapore, only 30.6% of patients were vaccinated with the influenza vaccine.[818] Another cross-sectional survey on 279 diabetes patients in Spain determined the vaccination rates for seasonal influenza, pneumococcus, and hepatitis B as 40%, 2%, and 2% respectively.[819] A survey on 274 elderly people in Turkey revealed that the proportion of diabetes patients vaccinated for influenza or pneumococcus or tetanus was 38.1%, 13.4%, and 9.28% respectively.[820]
- Perception, knowledge, and misconception that vaccines are infective and cause side effects are some of the barriers to avoiding vaccination.[818,819]
- Maintaining a diabetes registry, systemic tracking system, and reminder system serve as tools for improvising the acceptance to vaccination and communicating with the subjects for the need of vaccination which provides awareness on immunization.[819,821] The combined use of patient outreach letters, special immunization clinics, standing orders, and practitioner reminders on medical records resulted in a remarkable 15 fold increase in pneumococcal vaccinations in diabetes patients in Guam, United States.[822] Similarly, a combination of strategies including dissemination of guidelines, advice on setting up disease and vaccine registers, call and recall systems and benchmarking of performance remarkably improved influenza and pneumococcal vaccination rates in high-risk individual groups including diabetes patients in the United Kingdom.[823] Periodic training of the staff accompanied by ongoing

assessment of immunization rates and work flow and also a close follow up with the patient or his care giver by the treatment team is beneficial in minimizing the risk of inappropriate re-vaccinations.[824]

• The protocols should also aim at implementing a quality assurance process to maintain the standards of care.[825]

Implementation

Apart from the micro-and macro-vascular events in diabetes, infections due to influenza and pneumococci should be considered a significant public health concern. All clinics providing vaccinations shall maintain the records to assess the efficacy of vaccines regarding the occurrence of various complications in vaccinated individuals compared to non-vaccinated subjects. Vaccination strategies for diabetes should evolve as part of routine care, and a central registry must be maintained.

SEXUAL DYSFUNCTION

Recommendations

Recommended Care

- A detailed history and examination should be conducted in an unintimidating private setting with structured interviews by encouraging discussion regarding sexual concerns in both men and women with diabetes.
- Appropriate language considering the patient's age and culture should be used to make the patient comfortable.
- Psychological and social disturbances, if any, should be discussed in an empathetic manner.
- Promotion of lifestyle changes to reduce the associated risk factors should be encouraged in patients with diabetes of both sexes.

Men

- Prolactin and TFT levels should be considered before measuring testosterone.
- Testosterone levels should ideally be recorded in a good NABL lab, and should be done before 11 am, repeated if it is low. CBC PSA should be monitored thoroughly.
- Patients should be made to understand the difference between erectile dysfunction and premature ejaculation.
- Adult men with diabetes should be screened with a detailed sexual function history for ED as early as they are diagnosed with diabetes. Sexual history has to be taken during the first visit, along with the study of the frequency of sexual dynamics.
- Detection of ED and evaluation of the response to treatment should be performed by validated questionnaires such as IIEF or Sexual Health Inventory for men.
- PDE-5 inhibitors should be given based on the sexual frequency of the patient and may be offered as first-line therapy for the treatment of ED in men with diabetes as they improve the quality of life of the patients and are associated with low side effects.
- Symptoms of hypogonadism, including lack of interest in sex and ED should be investigated further with screening for serum testosterone concentration in the morning. Testosterone replacement may be beneficial in men with diabetes with symptomatic hypogonadism.
- Since psychogenic and organic components are also broadly responsible for ED, counselling should be recommended.

Women

- To identify whether a woman with diabetes has sexual dysfunction, eliciting a detailed history in a compassionate manner and examination is the first step.
- Several self-reported validated questionnaires such as Female Sexual Function Index, the Female Sexual Distress (FSD) Scale, the Brief Index of Sexual Functioning for Women, and the Derogates Interview for Sexual Function have been developed to assess FSD.
- Post-menopausal women with diabetes are prone to have a low desire or depression[826] and, mental health check-ups are recommended to rule out or manage the symptoms.
- Postmenopausal women, particularly those in the middle-age range, should be assessed for CV risk factors and FSD, so that both CVDs and sexual problems do not persist unnoticed.
- Currently, the therapeutic recommendations for FSD include maintaining a healthy lifestyle, achieving an optimal glycemic control, genitourinary infection control, and resolving psychosocial issues., And of course, Genitourinary hygiene.
- Treatment with water-based vaginal lubricants, hormone replacement therapy, clitoral therapy device, and genital infection control therapy is recommended.
- Treatment strategies with dehydroepiandrosterone supplementation, estrogen or androgen replacement, flibanserin (serotonin 1A receptor agonist and a serotonin 2A receptor antagonist), and PDE-5 inhibitors are investigated; however, currently there is limited evidence for their use.

Limited Care

- Adult men with diabetes should be screened with a detailed sexual function history for ED, as early as when they are diagnosed with diabetes.
- Symptoms of hypogonadism including lack of interest in sex and ED should be investigated further with screening for serum testosterone concentration in the morning.
- Promotion of lifestyle changes to reduce the associated risk factors should be encouraged in men with diabetes and SD
- To identify whether a woman with diabetes has sexual dysfunction, a detailed history and examination is the first step.
- Currently, the therapeutic recommendations for FSD include maintaining a healthy lifestyle, achieving optimal glycemic control, genitourinary infection control, and resolving psychosocial issues.

Background

Diabetes ensued vasculopathy and neuropathy have been associated with dysfunction of normal sexual function leading to psychosocial disruption and decreased quality of life in both men and women.[827–829] Sexual dysfunction (SD) in diabetics is a neglected aspect in India, primarily due to minimal communication time between physician and patient, lack of privacy during doctor visits and the taboo factor. In men with diabetes, erectile dysfunction (ED) as a result of autonomic neuropathy is commonly observed, and the prevalence odds compared with controls is more than 3.5 times.[830] In a study conducted in a hospital in New Delhi, Sondhi *et al*. observed the prevalence of ED to be 78.7% in men with T2DM versus 46% in non-diabetics and a significant correlation between duration of diabetes and ED.[831] Furthermore, the Massachusetts male aging study demonstrated that the risk of ED is double in aged diabetics versus the general population.[832] Diabetic neuropathy, impaired relaxation of cavernosal smooth muscle due to altered cyclic guanosine monophosphate/nitric oxide pathway and risk of decreased testosterone levels resulting from hypogonadism can constitute the underlying pathology of ED.[833,834] Other sexual complications in men with diabetes include ejaculatory dysfunction and hypogonadism. The recent ADA guideline recommends testing for serum testosterone concentration in men with diabetes who have symptoms of hypogonadism.[835]

Compared with men, SD in women with diabetes is rarely investigated and often untreated. In countries like India, where gender inequality and the cultural disparity are high, management strategies for tackling such health concerns are almost nonexistent.[836] However, the findings of a meta-analysis showed that the risk of female sexual dysfunction (FSD) was two times higher (OR [95%CI], 2.02 [1.49, 2.72]) and correlated with a low Female Sexual Function Index (FSFI) score in women with diabetes as compared with non-diabetics.[837] FSD is an intricate condition involving both physiological and psychosocial changes. It includes hypoactive sexual desire disorder, arousal and lubrication disorder, pain during sexual intercourse, and loss of ability to achieve orgasm.[838] Hyperglycemia decreases the hydration of the vaginal mucosa and lubrication of the vagina and is the cause of genitourinary infections and dyspareunia. The vascular complications and endothelial dysfunction may impact blood supply to the clitoris and lead to poor lubrication of the vagina and reduced arousal and dyspareunia.[827] Diabetic neuropathy may cause structural and functional changes in the female genitalia and can disrupt the balance between receiving sexual stimuli and sexual response triggers. Hormonal imbalances in levels of estrogen and androgens can lead to FSD in women with diabetes. In a study from North India conducted on women with diabetes, it was observed that 45.19% complained of desire disorder, 62.71% of arousal disorder, 84.75% of orgasmic disorder and 20.38% experienced pain disorder; the incidence of these disorders was higher in older women.[839]

Considerations

Gender, glycemic control, comorbidities, lifestyle management and knowledge of sexual disorders and their management, cultural environment, psychological disorders, and counselling should be considered when framing these recommendations for sexual dysfunction in patients with diabetes.

Rationale and Evidence

Men

- Longer duration of diabetes is considered a risk for ED.[831]
- Commonly associated comorbidities of diabetes including metabolic syndrome, obesity, hyperlipidemia, hypertension and autonomic neuropathy are also considered as risk factors of ED.[840]
- Anti-hypertensives, antidepressants and fibrates are frequent concomitant medications consumed by patients having diabetes and these are associated with increased risks of ED.[841]
- A significant association between ED and cardiovascular events, all-cause mortality, CHD and stroke has been reported in several studies.[842] Meena *et al*. observed an increased cardiovascular risk in patients with T2DM and ED without overt cardiovascular disease (CVD) in comparison to patients without ED (34.87 ± 18.82 vs 20.91 ± 11.03 p = 0.002).[843]
- Below normal testosterone concentrations and higher rates of hypogonadism have been reported in men with diabetes as compared with the general population.[844] Testosterone regulates normal erectile functioning and, evidence from studies suggests the use of testosterone replacement in patients with diabetes and symptomatic hypogonadism.[845] In a cross-sectional study conducted in India, the prevalence of hypogonadism was found to be 20.7%in T2DM patients.[846]
- Men with hypogonadism do not respond optimally to phosphodiesterase type (PDE)-5 inhibitors and in such patients, testosterone replacement was observed to be effective in 50% of patients.[845]
- Whether glycemic control has any effect on the reduction of ED risk is unclear as studies have shown contrasting results. However, intensive lifestyle changes ameliorated ED worsening and improved the overall International Index of Erectile Function (IIEF) score in overweight men with diabetes compared with controls in the LOOK AHEAD study.[847]
- Men with T2DM and severe ED were found to have poor glycemic control, longer duration of untreated diabetes, later age of onset and poor quality of life.[848]
- The ongoing TRAVERSE Trail findings will implicate determining the CV safety and long-term efficacy of testosterone treatment in middle-aged and older men with hypogonadism with or at increased risk of CV disease.[849]
- Ejaculatory dysfunction (EjD) constitutes significant sexual sequelae in diabetic men, with up to 35-50% of men with DM suffering from EjD. The main disorders of ejaculation include premature ejaculation (PE), delayed ejaculation (DE), anejaculation (AE) and retrograde ejaculation (RE). Whilst promising findings from large randomized controlled trials (RCTs) have provided strong evidence for the licensed treatment of PE, similar robust studies are needed to accurately elucidate factors predicting EjD in DM, as well as for the development of pharmacotherapies for DE and RE.[850,851]

Women

- Diabetes-induced neuropathy and vascular dysfunction may be mainly responsible for the FSD and the low Female Sexual Function Index may be associated with BMI.[670]
- Higher risk of FSD was observed in premenopausal as compared to postmenopausal women with diabetes.
- The risk factors associated with FSD include age, obesity, dyslipidemia, CVD, complications of diabetes, depression and marital status.[828,852]
- Based on the current evidence, a clear correlation between FSD and CVD has not been established unlike in men with diabetes.
- In women, psychological and psychosocial factors contribute to FSD more than in men.
- Social stigma around female sexuality remains and as a result, women often avoid and/or are embarrassed to discuss their sexual health with their health care professionals (HCPs). Moreover, midlife women are typically unaware or have misconceptions about conditions that may adversely impact their sexual life, such as genitourinary syndrome of menopause and hypoactive sexual desire disorder. Without understanding there may be underlying medical conditions, there is also a lack of awareness about the fact that safe and effective treatments are available.[850,853]
- According to the data of "The Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking (PRESIDE) study", involving 31,581 US women, sexual problems (desire, arousal, and orgasm) affect 43.1% of women. Hypoactive sexual desire is the most common dysfunction reported by 39% of women, low arousal by 26%, and orgasm problems by 21%.[854] In Europe, the "Women's International Sexuality and Health Survey" (WISHeS), conducted in 1356 women from Germany, United Kingdom, France, and Italy, reported a prevalence of FSD in 29% of women.[855]
- Sexual disorders in female patients with type 2 diabetes demonstrate the correlation with the occurrence of depression and the acceptance of their illness. Sexual disorders in diabetic patients occur more frequently in older women and in those with a longer duration of diabetes.[856]

In a study, 756 Adults with diabetes completed an online survey including questions on sexual functioning (adapted Short Sexual Functional Scale), general emotional well-being (WHO-5), symptoms of anxiety (GAD-7) and diabetes distress (PAID-20). One third of participants reported a sexual dysfunction. Men reported erectile dysfunction (T1D: 20%; T2D: 33%), and orgasmic dysfunction (T1D: 22%; T2D: 27%). In men, sexual dysfunction was independently associated with, older age (OR = 1.05, p = 0.022), higher waist circumference (OR = 1.04; $p < 0.001$) and longer duration of diabetes (OR = 1.04; p = 0.007). More men with sexual dysfunction reported diabetes distress (20% vs. 12%, p = 0.026). Women reported decreased desire (T1D: 22%; T2D: 15%) and decreased arousal (T1D: 9%; T2D: 11%). More women with sexual dysfunction reported diabetes distress (36% vs. 21%, p = 0.003), impaired emotional well-being (36% vs. 25%, p = 0.036) and anxiety symptoms (20% vs. 11%, p = 0.026).[857]

Implementations

Normal sexual function is essential for the holistic well-being of an individual. Diabetes with its ever-increasing prevalence is a cause of sexual dysfunction in both men and women. The vascular and neurological complications induced by diabetes constitute the underlying pathogenesis of these sexual dysfunctions. Association of diabetes with obesity, metabolic syndrome, hypertension, dyslipidemia and CVD are considered as risk factors for ED. The diagnosis of ED predicts further investigation of CV events in men with diabetes. Furthermore, symptoms of hypogonadism should be investigated by assessing the serum testosterone concentrations. A detailed history of FSD obtained in a compassionate and structured method is essential in women with diabetes. Although, limited evidence exists to show correlation between FSD and CV events, lifestyle modifications, glycemic control, care of genetic infections and resolution of psychosocial factors should be discussed and emphasized.

It becomes clinically relevant to assess particularly postmenopausal women for FSD and CVDs, since both disorders still remain underdiagnosed and sub-optimally untreated. Clitoral Doppler ultrasound could represent a useful technique to diagnose the presence of underlying CVD, which along with risk factors could predict sexual dysfunction in women.

A mention about possible relationship between CV disease and ED in men having T2DM will be justified based on robust evidence necessitating CV risk assessment and/or screening for ASCVD in male patients having T2DM and ED.

CLINICAL MONITORING RECOMMENDATIONS

Recommended Care

- Monitor blood glucose control by measuring HbA1c using high-precision methods standardized and aligned to the international reference values.
- Self- Monitoring Blood Glucose (SMBG) enables patients to confirm symptomatic hypoglycemia and detect asymptomatic hypoglycemia and glucose variability. It facilitates making appropriate adjustments in treatment medications and nutrition therapy to achieve HbA1c targets and prevent hypoglycemia.
- In patients on insulin, a combination of HbA1c and SMBG helps achieve glycemic control.
- Measure HbA1c every three to six months depending on level, stability of blood glucose control, and changes in therapy and report HbA1c results in percentages.
- Advise individuals with diabetes that maintaining an HbA1c <7.0% minimizes the risk of developing complications.
- A lower value of the HbA1c target may be considered if it is quickly and safely achieved without hypoglycemia.
- A higher value of the HbA1c target may be considered for individuals where previous attempts to optimize control were associated with unacceptable hypoglycemia or in those individuals who are at a higher risk for hypoglycemia.
- Treatment should be reviewed and modified if the HbA1c level exceeds the agreed target on two consecutive occasions.
- Advise those who target HbA1c levels cannot be reached that any improvement is beneficial.
- Anemia must be excluded before a proper diagnosis based on HbA1c values is made. Anemia and abnormal hemoglobin may affect the values obtained for HbA1c in some assays. To determine whether abnormal hemoglobin is present, use high-performance liquid chromatography or mass spectrometry. In individuals with hemoglobinopathies, fructosamine may be used as a surrogate.
- Point-of-care capillary blood glucose meters should be used to measure blood glucose when patients are hospitalized. Blood glucose meters conforming to the latest ISO standards should be used.
- When prescribing continuous glucose monitoring or ambulatory glucose profile (CGM/AGP), robust diabetes education, training, and support are required for optimal continuous glucose monitor implementation and ongoing use.

Limited Care

- If HbA1c measurement is unavailable, blood glucose should be measured either at point-of-care or in the laboratory.
- In limited resource settings, diabetes control may need to be based on measuring plasma glucose levels alone.

Background

Monitoring the glycemic status is critical to ensure optimum glycemic control. It is a cornerstone of diabetes care that may help physicians to adjust the treatment regime according to patients' needs and allow patients to follow the prescribed diabetes care.850 Glycated hemoglobin (HbA1c), which assesses the glycosylation of the hemoglobin to an estimated level of blood glucose over the previous three months, and self-monitoring of blood glucose (SMBG), which records the day-to-day blood glucose levels, are the two most essential tools for monitoring of glycemic control.851 Measurement of HbA1c is a gold standard approach for monitoring diabetes in research and clinical settings.852–854 Most guidelines recommend clinicians must perform HbA1c measurements routinely in all patients with T2DM as a part of continuing care.855,856 Long-term hyperglycemia, as measured by HbA1C, is associated with a higher risk of secondary macro-and microvascular complications of diabetes.857,858 Patients with diabetes who do not reach appropriate glycemic targets or are at an increased risk of developing complications require more intensive monitoring. Further, in Asian countries like India, cultural aspects of weekly fasts, festivals, a diet rich in carbohydrates, and reluctance to change dietary habits further support the need for regular glucose monitoring. Frequent SMBG,852,858 continuous glucose monitoring (CGM), 859,860 assessing impending glucose excursions (hypoglycemia and hyperglycemia), and glycemic variability861 are some of the methods of intensive glucose monitoring.

SMBG is an essential component of modern diabetes treatment; it is the most straightforward and possibly most practical tool to assess the efficacy and safety of glycemic control.851,862 SMBG facilitates patients and healthcare providers to adjust their therapeutic regimen in response to blood glucose values and regulate their dietary intake, physical activity, and insulin doses to improve glycemic control regularly.858,863 Established advantages with SMBG include achieving target HbA1c, reducing glucose variability, and predicting severe hypoglycemia.863 SMBG complements HbA1c testing as it can differentiate the fasting, pre-prandial, and post-prandial hyperglycemic levels, detect the glycemic excursions, recognize and contribute to monitoring and resolution of hypoglycemia, and provide immediate feedback to patients about the effects of food choices, activity, and medication on glycemic control.864

The International Diabetes Federation (IDF) and American Diabetes Association (ADA) recommend SMBG as an integral component of effective T2DM management.7,857 Despite substantial evidence of the benefits of SMBG, compliance to self-monitoring is reported "low" globally,865 particularly in developing countries like India, where patients usually seek treatment after complications have set in. This may be attributed to a lack of awareness, literacy levels, and perception that SMBG is painful and costly.866

CGM has fulfilled an unmet need in diabetes care by providing an option of automated glucose monitoring, which may help improve glucose control in patients with uncontrolled T2DM and patients on acute and intensive glucose lowering regimens. The current recommendations provide insight into the importance and frequency of monitoring to facilitate medication and lifestyle changes when average HbA1c values remain above target levels.

Recommendations for Glycosylated hemoglobin for monitoring blood glucose:

- Regular monitoring of HbA1c will facilitate the identification of patients with poor glycemic control and help physicians and patients to take the necessary steps to achieve desired glycemic targets867,868 Though frequent monitoring of HbA1c is associated with reduced diabetes-related complications and improved metabolic control,868,869 most patients do not understand or are unaware of the importance of glycemic monitoring. Therefore, it is vital to educate patients and improve their understanding of HbA1c levels for optimal glycemic control. 868,870
- The concept of estimated average glucose (eAG) was introduced following continuous ambulatory blood glucose monitoring.871The eAG may help people with diabetes relate their HbA1c to daily glucose monitoring and highlight any inaccuracies in HbA1c measurement relative to glucose levels.872 Calculators are available for converting HbA1c to eAG in both mmol/L and mg/dL. Measurement of glucose levels, before meals, after meals, and fasted state are often recommended as a substitute for HbA1c when the latter is unavailable or inappropriate.
- Abnormal hemoglobin levels are known to affect HbA1c values in a way that can significantly alter the results concerning diabetes control.873 Therefore; it is crucial to consider hematological factors that can confound HbA1c levels in people with diabetes; best detected using HPLC-based assays or measuring surrogates like Fructosamine.
- Anemia significantly impacts HbA1c levels. In a cross-sectional study, the mean HbA1c in patients with controlled diabetes with Iron Deficiency Anemia (IDA) was considerably higher than in those without IDA (7.86 ± 0.11% vs. 5.45 ± 0.038% [$p<0.05$]) and the HbA1c values were inversely proportional to total hemoglobin ($p<0.05$).874
- Further, significantly higher HbA1c levels are observed in patients with IDA than in healthy individuals (5.51 ± 0.696 v/s 4.85 ± 0.461%, $p<0.001$), and the HbA1c levels significantly decline following iron supplementation ($p<0.001$).[10] Therefore, HbA1c results in diabetes patients with IDA should be interpreted carefully. Ideally, IDA has to be corrected before a proper diagnosis is made.

- Measuring blood glucose using blood glucose meters on admission to hospital wards help identify patients with hypoglycemia or hyperglycemia. Considering that in developing nations like India, where cost is a significant barrier to monitoring, these devices should be accurate and cost-effective and field testing tailored explicitly for Asian and Indian needs is imperative.875
- A study that assessed knowledge and attitude towards self-monitoring and the impact of SMBG on glycemic control revealed that patients who monitored ≥3 times had significantly better glycemic control of HbA1c (7.1–8%) than those who monitored <3 times (p=0.021).876 Insulin self-titration interventions based on structured SMBG are associated with a significant reduction in HbA1c during a follow-up of 12 weeks with a trend towards greater effectiveness in improving glycemic control than conventional treatment, with no increase in the incidence of hypoglycemia or body weight gain.877 Comparative studies in patients with T2DM on insulin across cohorts of regular SMBG users versus SMBG non-users have demonstrated that HbA1c levels in regular SMBG users were lower by 0.7-1.1%.865,878–880

Target values for glucose control for HbA1c and capillary blood glucose for diabetes, as described by the IDF 2017, are as follows881[Table 21].

Table 21: Target values for glucose control for glycosylated hemoglobin in non-pregnant adults

	Targets	Targets, if possible, to achieve without causing hypoglycemia.
HbA1c (%)	<7.0	<6.5
Fasting Blood Glucose(mg/dL)	115	<100
Post-prandial blood glucose (mg/dL)	160	<140
DM: Diabetes mellitus, FPG: Fasting plasma glucose, HbA1c: Glycosylated hemoglobin, IGT: Impaired glucose tolerance, PPG: Postprandial glucose, T2DM: Type 2 DM		

Recommendations for self-monitoring of blood glucose [Tables 22 - 25]

- Selecting a structured, flexible SMBG pattern that can be tailored to the clinical, educational, behavioral, and financial requirements of individuals with diabetes is recommended.851 It is essential to determine the frequency and intensity of SMBG needed to support the chosen treatment regimen. One should also consider practical obstacles to monitoring, such as affordability or access, individualize glycemic targets and modify monitoring patterns accordingly.882,883
- Individuals with insulin-treated diabetes should be advised to perform SMBG daily, failing which, at least weekly monitoring should be encouraged. Pre-meal SMBGs help guide the prandial insulin dose. Fasting blood glucose readings help guide the basal insulin dose. Ideal SMBG: six to seven tests/day, i.e., three before and three after each meal every day and periodically, one additional test at 3 am.851
- In addition, SMBGs in motivated patients may help identify and correct dietary preferences. Monitoring and documenting diet patterns and SMBG recordings may be recommended in such cases.
- Pregnant women on lifestyle modifications should have a daily profile weekly. This should include one fasting and three post-prandial values at least once a week or staggered over a week. 851
- Pregnant women with diabetes who are on insulin may need to monitor their blood glucose more frequently, i.e., 4-6 times/day.
- In patients with pre-existing diabetes or GDM, target blood glucose levels should be 70 to 90 mg/dL fasting, <140 mg/dL 1-h post-prandial, and <120 mg/dL 2-h post-prandial.
- In elderly patients, the frequency of SMBG should be once daily (different times each day) in the initiation phase, and later it should be reduced further to two to three times per week.

Considerations

The decisions on clinical monitoring of glycemic levels in T2DM patients were based on local factors such as the availability of newer technologies and the cost of monitoring that were reviewed in the Indian context (Table 26).

Rationale and Evidence

Table 22: Recommended care for frequency/timing of SMBG 851

T2DM on OADs		**T2DM on insulin or insulin + OADs**	
New onset/uncontrolled/ during acute illness	**Stable/well-controlled**	**New onset/uncontrolled/ during acute illness**	**Stable/well-controlled**
Patients on SU or meglitinides: At least four times/day and should include pre-prandial and bedtime levels. Patients on other OADs: At least FBG on alternate days.	At least four tests in a week on four consecutive days or alternate days (including an FBG and three postprandial values).	At least four times/day and should include pre-prandial and bedtime levels. Must check whenever hypoglycemia is suspected.	Paired testing at least 3-4 days in a week (1 day/ week pre- and post-breakfast, one day/week pre- and post-lunch, and one day/week pre- and post-dinner) or as frequently as possible. Must check whenever hypoglycemia is suspected.
FBG: Fasting plasma glucose, OADs: Oral antidiabetics, SU: Sulphonylureas, DM: Diabetes mellitus, T2DM: Type 2 DM			

Those who drive must measure sugar before the start of the journey to ensure it's more than 90 mg/dl and preferably every 2 hours after that during the trip. Periodic carbohydrate snacking is recommended. To stop the car engine, take out the keys and move to the non-driver's seat if they feel hypoglycemic, measure blood sugar, and if it's below 90 mg/dl, to have simple carbohydrates. Not to drive for at least 45 minutes after recovery. Anyone who is an Insulin user or on drugs that are known to cause hypoglycemia like Sulfonylureas or meglitinides should record their blood glucose on a glucometer which has memory and can store readings for up to last three months (to be reviewed by the physician).

Table 23: Recommended care for frequency/timing of self-monitoring of blood glucose for diabetes in pregnancy 851

Patients on lifestyle modifications	**Patients on OADs or insulin**
A day profile once a week-FBG and three postprandial values at least once a week or staggered over the week.	At least four times/day (FBG and three postprandial values).
FBG: Fasting plasma glucose, OADs: Oral antidiabetics	

Plasma Glucose measurement in laboratories: Plasma glucose is the most preferred measure in most modern laboratories. Readings based on whole blood measurements are lower due to the volume occupied by hemoglobin. Capillary blood glucose strips measure the glucose in the plasma of the capillary blood sample. Still, they may be calibrated to give results as plasma or whole blood glucose (check meter instructions).

Recommendations for Continuous glucose monitoring

The recent availability of retrospective and real-time continuous glucose monitors has opened a new dimension to diabetes care. In affording

patients who can afford technology, CGMs can improve diabetes care by achieving glycemic targets by identifying and implementing measures to avoid glycemic excursions.

In exceptional cases such as pregnant women, patients on multiple daily insulin doses, and children and adolescents, CGM may help adjust prandial insulin doses and other dietary decisions.884 with the convenience of avoiding finger pricks.

• Garg *et al*. have demonstrated an improvement in glycaemic excursion in insulin-treated T2DM patients using Real time-CGM, showing a significant reduction of the time spent in the hypo- and hyper-glycaemic range with an increased time spent in the target glucose range as well as a significant reduction of nocturnal hypoglycemia in the Real time-CGM group.880

• Mohan *et al*., evaluating the use of retrospective CGM, concluded that it could effectively help healthcare professionals with insights for initiating changes to treatment regimens, diet, and exercise behaviors and provided patients with improved knowledge of the importance of therapy compliance by demonstrable reductions in HbA1c.885

• A retrospective analysis based on a blinded study of glycaemic control in 296 T2DM adults using masked professional CGM (P-CGM) revealed that the predominant pattern of hyperglycemia was postprandial while previously unknown hypoglycemia was found in 38% of the patients; over half of the cases were nocturnal. The mean HbA1c of the P-CGM group significantly dropped at six months from baseline ($P < 0.0001$). The frequency of performing SMBG was also found to be substantially increased. P-CGM motivated the patients for diabetes self-care practices, improving glycaemic control over a wide range of baseline therapies.886

In resource-limited settings, given the high cost, the use of the CGM devices is compromised till the date of publication of this document.

Implementations

There should be access to a laboratory or site-of-care test monitored by certified quality assurance schemes to measure HbA1c. In instances where HbA1c measurement is inappropriate, such individuals must be identified by carefully reviewing hematological parameters and other factors affecting HbA1c values. The provision of capillary blood glucose meters and strips must be assured in hospitals and clinics. It is vital to ascertain whether there are contraindications to using a particular type of glucose meter for a specific patient. It is essential to establish whether glucose meters report values for plasma or blood and to ensure that schemes for monitoring the quality of their output are in place. Blood glucose meters should be calibrated regularly, used in hospitals, and restricted to trained personnel.

Table 24: Recommendations for glycemic targets in people who are prone to develop Hypoglycemia (associated with Renal, Hepatic, or CVD risks) 882,883

Target glycemic levels	Patients on hypoglycemic agents	Patients with intermediate health status	Patients with poor health status
HbA1c (%)	< 7.5	< 8.0	< 8.0
Fasting or pre-prandial glucose (mg/dL)	90-130	65	100-150
Bedtime glucose (mg/dL)	90-150	150-180	150-220
HbA1c: Glycosylated hemoglobin			

Table 25: Limited care for frequency/timing of self-monitoring of blood glucose

	New onset/uncontrolled/DM during acute illness	Stable/well-controlled
T2DM on OADs	Patients on SU or meglitinides: At least FBG alternate days. Patients on other: Ideally, at least FBG once a week.	At least four tests in a month-at least 1 test/week (including an FBG and three postprandial values in a month).
T2DM on insulin or insulin + OADs	At least FBG and one more pre-prandial value every day. Must check whenever hypoglycemia is suspected.	At least one value on alternate days at different times of the day, with at least one FBG every week. Must check whenever hypoglycemia is suspected.
	Patients on lifestyle modifications	**Patients on OADs or insulin**
Diabetes in pregnancy	One FBG and one postprandial value every week (any meal, preferably the largest meal of the day).	Paired testing every day (pre- and post-breakfast on 1st day, pre- and post-lunch on 2nd day, pre- and post-dinner on 3rd day, and then keep repeating the cycle). Post-delivery, an FBG and HBA1c are recommended for all GDM patients.
Patients on basal insulin	In resource-limited settings, fasting levels can be performed twice a week or once in 3 days.	

DM: Diabetes mellitus, FBG: Fasting blood glucose, OADs: Oral antidiabetics, SU: Sulphonylureas, T2DM: Type 2 DM

Table 26: Other aspects of clinical monitoring

Type of monitoring	Recommended care	Limited care
Complete history and physical examination	A complete history (including- presenting complaints, medical conditions, diet, lifestyle, habits, family, medication, and physical examination is recommended Periodicity: At diagnosis or first visit and then Annually.	As for recommended care.
Anthropometry	Weight, waist circumference/BMI	
Ophthalmic	Detailed exam by a qualified ophthalmologist or fundus photographs (with in-person or AI-based interpretation by skilled ophthalmologists). Periodicity: At diagnosis and every two years if there is no retinopathy Reasons for: Immediate referral: • Rubeosis iridis/neovascular glaucoma • Vitreous hemorrhage • Advanced retinopathy with retinal detachment Urgent Referral: (<2 weeks) • R3/Proliferative retinopathy • Routine referral: (<13 weeks) • R2/Pre-proliferative changes • M1/Maculopathy • Routine non-DR referral: • Cataracts Other categories; • R0/No retinopathy-annual screening, moving to 2 years if two negative screens.	Patients are to be referred to ophthalmologists if retinopathy is suspected.

	• R1/background retinopathy-annual screening and inform diabetes care team.	
Smoking cessation		As for recommended care
Alcohol	Counseling for moderation	As recommended for care
BP measurement	BP measurement at each visit	As for recommended care
Measurement of lipids	At diagnosis or age 40 years and periodically (6 monthly) after that	At diagnosis or age 40 years, at least
Screening for CVD	A resting ECG may provide helpful information on baseline cardiac status and (for future reference) 2d ECHO when required	As for recommended care
Microalbuminuria	At diagnosis, after correcting glycemia and achieving BP Goals, and annually after that.	If resources are limited and technical issues may consider using ACEI/ARB. If BP is >140/80 Dipsticks for MA can be used. Every patient's urine should be examined routinely and microscopically.
Distal peripheral neuropathy	At diagnosis and at least annually Test for vibration with a 128 Hz tuning fork or a 10 g monofilament, or with Biothesiometer or Neurothesiometer (VPT) along with pinprick sensation and ankle jerk.	As recommended by IDF, Additional training is required.
Peripheral arterial disease	At diagnosis History of claudication, distal pulses, and ABI, Foot doppler.	As for recommended care Additional training required
Comprehensive foot care	At diagnosis and annually. Assessment of foot pulses and testing for loss of protective sensation (10 g monofilament plus testing any one of Vibration using 128 Hz tuning fork, pinprick sensation, ankle reflexes, or vibration perception threshold). Look for calluses, ulcers, and foot deformities.	As for recommended care, Additional training is required.

BP: Blood pressure, CV: Cardiovascular, CVD: CV disease, ECG: Electrocardiogram, ABI: Ankle-brachial index, ACEI: Angiotensin-converting enzyme,
ARB: Angiotensin receptor blocker, IDF: International Diabetes Federation

TECHNOLOGIES

Recommendations

Recommended Care

Continuous glucose monitoring (CGM)

- CGM should be considered in conjunction with SMBG and HbA1C for glycemic status assessment in those T2DM individuals treated with intensive insulin therapy and who are not achieving glucose targets.[895]
- Two types of CGMs are available. The professional or retrospective (blinded) CGM which records the data that can be downloaded later in a physician's office and the personal or prospective (Real-time) CGM which displays the interstitial glucose values with continuous basis.
- CGMs can be a helpful tool in diabetes education by facilitating effective communication between clinicians and patients. All users should get trained on how to interpret and respond to their glucose data.[896]
- AGP Report along with %TIR, %TBR, %TAR, and daily glucose pattern may be used for education and motivation of patients living with diabetes.[897]
- 14 days of CGM is required for the assessment of Time in the Range of which at least 70% of the data should be available.
- In well-controlled T2DM, professional CGM once in 6 months could be sufficient irrespective of the treatment regimen. If the %TIR is low or %TBR is significantly high then CGM may be repeated more frequently based on the clinical judgment and availability of resources.[898]
- CGM may be considered in women with GDM or pregnant women with T2DM and as a supplemental tool to SMBG in individuals with hypoglycemia unawareness and/or frequent hypoglycemic episodes.
- Only CGM systems with an acceptable level of sensor accuracy should be used and when assessing hypoglycemia, the accuracy of the CGM data in the lower glycemic range should be considered and hypoglycemia conformed by SMBG where needed.

Continuous subcutaneous insulin infusion (CSII) or insulin pump therapy

- CSII or insulin pump therapy may be considered in pediatric patients or in adults on ≥4 insulin injections per day (intensively managed insulin-dependent T2DM).

Common indications are:

- High HbA1C levels despite MDI
- Recurrent episodes of hypoglycemia or hypoglycemia unawareness
- Patients on high doses of insulin or poor glycemic control despite intensive therapy
- Presence of or future risk of diabetes-related complications, or recurrent DKA/recurrent hospitalizations
- Dawn phenomenon
- Glycemic variability causing challenges in diabetes management
- Unpredictable food or meal intake patterns
- Patients seeking improved quality of life
- Insulin pump therapy seems to be safe and effective for maintaining glycemic control and for better outcomes in pregnancies complicated by GDM/ T2DM and requiring large insulin doses. However, it is not recommended as a part of routine practice.
- During hospital admissions, CSII is not recommended in critically ill patients if the hospital/ICU staff is not familiar with the device
- In non-critically ill patients, continued use of CSII is recommended if the patient can manage the use of the device himself or has trained assistance for the same.
- CSII should be prescribed to only those eligible patients who are willing and motivated to monitor glucose levels at least four times a day, quantify food intake, and comply with follow-up. Patients must be psychologically stable and in the case of young candidates, they should have adequate support from motivated caregivers who can learn and can commit to the different aspects of diabetes management.
- CSII should only be initiated at a well-equipped center that has trained resources to initiate and follow up the patients on CSII or centers willing to acquire the training and expertise.
- AID: Automated Insulin Delivery devices such as 780G though very expensive may be used in eligible subjects, for automating both basal and bolus insulin delivery based on sensor glucose levels.
- Continuous training and retraining would be required to learn the techniques and excel in CSII management.
- Change of cannula insertion site as per manufacturer's label should be recommended.

Clinical decision support tools and diabetes management platforms

- Technologies that aid patients and/or healthcare providers in the diagnosis and management of diabetes can improve both the short-term and long-term disease outcomes.
- Adequate training needs to be provided to the healthcare professionals in using the clinical decision support tools and diabetes management platforms.
- From among the various diabetes self-management tools and platforms available, patients must be encouraged to adopt the most appropriate tool that would best suit their disease needs and lifestyle.

Patients must be encouraged to seek timely guidance and frequent reassessment from a trained healthcare team and must be made aware that the adoption of various diabetes self-management tools does not diminish the importance of the former.

Table 27: Recommendations on the technologies suggested for recommended care and limited care

Technology	Recommended Care	Limited Care
Glucose meter (SMBG)	Yes	Yes
Diabetes Apps	Yes	Yes
Insulin pump	Yes; indications should be discussed and apart from usual indications, CSII as an option to improve the quality of life of the individual should be discussed.	Can be discussed when there is a compelling indication
CGM	Yes; indications should be discussed	Can be discussed where affordability is not an issue.

Background

Technology has gradually become indispensable in the management of diabetes. Various different technologies are now being routinely used for monitoring, drug delivery, improving clinical decision support, compliance and adhere to lifestyle changes and therapy.

Continuous glucose monitoring (CGMs) and Continuous subcutaneous insulin-pump infusions (Insulin pumps) have limited reach yet in India, but glucose meters (SMBG), telemedicine and mobile apps may be cheaper options for enhancing adherence to therapy, enable coaching with an aim to improve metabolic outcomes and reach goals of management.

There have been a few guidelines, consensus and recommendations both internationally, as well as specific to Indian scenario regarding the use of various technologies, its use and limitations, its merits and challenges, and guidance on recommended care and limited care in resources restricted situations, all aimed at improving lives of people with diabetes and preventing complications of diabetes.

Rationale and Evidence

Blood glucose meters

SMBG with a quality glucose meter has been proven to be useful at any stage of diabetes provided a structured SMBG protocol is implemented with the patient-centered approach. Glucose monitoring, particularly SMBG is considered as an integral part of diabetes care[899–902] since achieving optimal glycemic control has been proven to be associated with reductions in both macro-and microvascular complications of the disease.[903–905] SMBG has been demonstrated to be helpful or to correlate with effective management in both insulin-treated and noninsulin-treated diabetes.[900,904,906–910] Many different models of glucose meters are available to suit the needs of the patients and differ in terms of their accuracy, amount of blood needed for each test, ease of use, pain associated with using it, testing speed, overall size, memory functions to store the test results, the likelihood of interferences, the ability to transfer data, procurement costs of the meter and accessories, special features such as automatic timing, error codes, large display screen, etc.[911] Regarding the accuracy of the glucose meters, though there are several current standards, the most commonly followed are those of the International Organization for Standardization (ISO 15197:2013)[912] and the U. S. Food and Drug Administration (USFDA).[913–915] Currently connected glucose meters provide a patient-friendly visualization of blood glucose trends, time spent in range, time spent in hypoglycemia, cloud storage, ability to email the digital blood glucose diary to the physician's office along with storing the entire information. These glucose meters also provide options for users to enter data on insulin and other medications, calculate insulin carb ratio, and insulin correction factor etc. thereby providing a comprehensive digital solution to a motivated patient. SMBG continues to be the most important tool to pick up hypoglycemia accurately and all patients with diabetes should be trained and encourages to use the glucose meter regularly through the frequency may differ based on individual needs, nature of therapy, available resources and glucose profiles.

Continuous glucose monitoring systems

All CGM systems have one goal: providing glucose monitoring data for optimizing lifestyle interventions and pharmacotherapies for preventing blood glucose variations also measures interstitial fluid glucose and CGM system involves using devices and sensors attached to a body part (arm/abdomen) with a variable life of 7-14 days. This may also require calibration of using an SMBG device.

Types of CGMS devices

- Retrospective systems that measure the glucose concentration during a certain time span: The information stored in the sensor can be downloaded using a monitor. They first record the glucose levels, providing retrospective information of the overall glycemic profile, without a RT display of glycemic value. In fact, it allows to evaluate the glycemic profile in patients with poorly controlled diabetes, detecting and preventing unrecognized hypoglycemic events, identifying glycemic patterns and trends which permit changes in pharmacotherapy with physical and dietary interventions.
- Real Time systems that continuously provide the actual glucose concentration on a display: RT monitoring shows directly to the patient the glucose levels in RT. It may provide alarms when glucose values in case of extremes at pre-defined preset values to prevent severe hyper and hypoglycemia frequency. Some of the RT systems may require intermittent scanning of sensor (min once in 8 hours) to be able to record and display the RT data on a continuous basis (isCGM- *intermittent CGM*).

Recommendations for CGMS

1. Clinical situations that may require greater glucose monitoring accuracy
- History of severe hypoglycemia
- Hypoglycemia unawareness
- Pregnancy
- Infants and children receiving insulin therapy
- Patients at risk for hypoglycemia, including patients receiving basal insulin
- Patients receiving basal-bolus insulin therapy with multiple injections per day
- Patients receiving sulfonylureas or glinides (insulin secretagogues)
- Patients with irregular schedules skipped or small meals, vigorous exercise, travel between time zones, disrupted sleep schedules, shift work
- People with occupational risks that enhance possible risks from hypoglycemia (for example, driving or operating hazardous machinery).

2. RT-CGM alone is not recommended for glucose management in the intensive care unit or operating room until further studies provide sufficient evidence for its accuracy and safety[916].

3. CGM is widely used to evaluate the effectiveness of different therapeutic approaches in the management of T2D and also to compare the effectiveness of the different oral hypoglycemic agents [917]

4. CGM is widely used to assess other issues related to T2D, as to evaluate frequency and severity of the dawn phenomenon in non-insulin-treated T2D patients across different age categories[917]

5. RT-CGM devices is recommended in adult patients with T1DM irrespective of any values who can afford and use these devices on a nearly daily basis.[916]

6. Real-time CGM (rtCGM) A or intermittently scanned CGM (isCGM) B should be offered for diabetes management in adults with diabetes on multiple daily injections (MDI) or CSII who are capable of using devices safely (either by themselves or with a caregiver). The choice of the device should be made based on patient circumstances, desires, and needs.

7. The intermittent use of CGMSs designed for short-term retrospective analysis may be of benefit in adult patients with diabetes to detect nocturnal hypoglycemia, the dawn phenomenon and postprandial

hyperglycemia and to assist in the management of hypoglycemic unawareness and when significant changes are made to their diabetes regimen (such as instituting new insulin or switching from MDI to pump therapy).
8. CGMS device has been used to assess the effect of acute psychological stress in T2D [917]

Continuous subcutaneous insulin infusion

Insulin Pump Therapy (IPT)

Insulin pumps are meant for Continuous Subcutaneous Insulin Infusion to mimic physiological delivery of insulin. Insulin pumps unlike conventional syringes and pens offer a plethora of benefits. Over the last two decades, insulin pumps have undergone significant technology advancements. The indications and contraindications of insulin pump therapy is the physicians' discretion and based on published guidelines. Selection of the subject is an important criterion to ensure not only success but also to avoid the possible hazards of using this technology.

Sensor Augmented pumps

Sensor augmented pumps wirelessly connect with CGM; the earlier devices were only capable of eliminating hypoglycemia to an extent. Standalone pumps may be used along with SMBG or CGM and currently have limited application.

Automated Insulin Delivery Systems

The new automated insulin delivery devices, with the help of an integrated algorithm, has been successful in reaching a TIR of around 80% eliminating both hypoglycemia and hyperglycemia by changing the basal rates every 5 minutes in response to sensor glucose levels. The new Automated Insulin Delivery (AID) system available in India is even capable of delivering auto bolus doses if the algorithm decides so.
Every eligible candidate with T1D may be offered the best advanced delivery device fulfilling the criteria for selection.[918,919]

Insulin pumps for type 2 diabetes

For type 2 diabetes and other types of diabetes, there is evidence that insulin pumps could be beneficial not only in maintaining TIR targets but also in managing neuropathy, erectile dysfunction etc.[920–922] Physicians may follow the recommendations for choosing the right candidates for IPT.[923]

Training and Troubleshooting

Insulin pumps and AID require intense training, troubleshooting and follow up by the multidisciplinary team for several months after initiation.[924] The merits and demerits need to be discussed in detail with the patient or caregiver for a shared decision making while choosing this option.[925]

Do-It-Yourself Closed-Loop Systems (DIY)

DIY is not approved by any scientific organization or by the US FDA. However, there are thousands of patients who have created their own Artificial Pancreas with compatible pumps, CGM devices, and downloadable algorithms. Even ADA suggests all clinicians have a knowledge on DIY AP to troubleshoot as and when required and should never discourage patients from using it due to the possible benefits.[926,927]

Recommendations[923]

1. Standardized, single-page glucose reports from CGM devices with visual cues, such as the ambulatory glucose profile (AGP), should be considered as a standard summary for all CGM devices.
2. In addition to being associated with microvascular complications, IR can also be used to assess glycemic control. For evaluating the treatment regimen, time below target and time above target are also useful parameters.
3. It is crucial for diabetics/caregivers to receive initial and ongoing education and training, whether they are receiving it in person or remotely, as well as regular evaluation of technique, results, and the ability of the patient/caregivers to adjust the therapy based on data, including uploading/sharing (if applicable).
4. When used as an adjunct to pre- and postprandial BGM, CGM can help to achieve A1C targets in diabetes and pregnancy.
5. Periodic use of rtCGM or isCGM or use of professional CGM can be helpful for diabetes management in circumstances where continuous use of CGM is not appropriate, desired, or available.
6. Skin reactions, either due to irritation or allergy, should be assessed and addressed to aid in the successful use of devices.

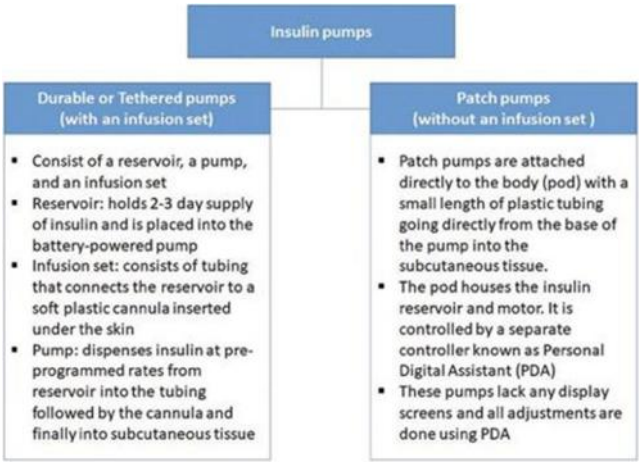


Figure 16: Types of insulin pumps[928–930]

Technologies to improve clinical decision support and treatment compliance

The overall quality of diabetes care still remains suboptimal due to various patient and provider-related factors. An organized, systematic approach to diabetes self-management and continued support from a trained multidisciplinary diabetes care team are thus highly crucial for achieving optimal outcomes.[931,932] Many solutions have been identified or are being employed to achieve this such as redesigning the organization of the care process, empowering and educating patients, implementing clinical decision support systems such as electronic health record tools, using diabetes detection or management apps and platforms for patients and healthcare professionals, etc.[931,933,934]
Clinical decision support systems (CDSS) are applications that can analyze data and aid healthcare providers to make clinical decisions and improve patient care. Classic CDSSs may include various features like alerts, reminders, order sets, drug-dose calculators, etc. that automatically remind the doctors of a specific action, or care summary dashboards that provide performance feedback on quality indicators thereby ensuring patient safety and improved health outcomes. Both commercially and locally developed CDSSs are effective at improving healthcare process measures across diverse settings.[935,936]
Telemedicine is a disease management strategy whose basic concept matches that of a CDSS. With the aid of telecommunications, telemedicine facilitates remote delivery of health-related services and clinical information.[937] Various telemedicine modalities have been proven to be effective and safe across various patient populations irrespective of their type of diabetes. They have been also associated with time savings, cost savings, high appointment adherence rates, and high patient satisfaction. In populations with limited access to care, telemedicine effectively improves the overall disease outcomes.[938–942]

Limitations

Use of diabetes technology depends on availability of technology, cost, needs, desires and skills of persons living with diabetes and their caregivers. Lack of proper education, training and follow up can limit the intended benefits of diabetes technology. People using CGM devices will still need BGM for reasons ranging from calibration to rapidly changing glucose levels. Wide adoption of CSII and RT-CGM is limited by cost, psychosocial, and educational factors[943].

Contact dermatitis/Allergy has been reported with CGM/Pump. Digital health technology (Internet, monitoring, coaching, connection, lifestyle apps) only from reliable and verified resources backed by clinical evidence and real-world performance/outcomes should be used. Limitations may range from inadequate evidence on app accuracy, clinical validity, lack of training provision, poor interoperability, standardization, and insufficient data security[944]. Lack of insurance coverage on advanced digital technologies and devices may also restrict their use in India[945].

Future of Technology in Diabetes

The use of technology in the management of PwD is increasing at a rapid pace due to proven benefits. Several new frontiers are being explored and a number of new technology-based products are in the pipeline.

Digital Therapeutics – These are the products that deliver evidence based therapeutic interventions to patients that are driven by high quality software programs to prevent, manage or treat a medical disorder or disease. These products have been shown to improve patient compliance, therapeutic success and economic outcomes in the management of PwD[946].

Self-care & Wellness apps – Several mobile applications that help the patients in monitoring their vitals, calorie intake, activity etc. are currently available. These are useful for calorie counting, carb counting, calculating insulin doses, tracking daily activity, tracking the glycemic profile. Utmost care should be taken while recommending any such apps to the patients with regards to its accuracy and data security.

Non-Invasive Glucose Monitors – Various non-invasive glucose monitoring devices have already been introduced in the market and many more are currently being developed. There is no sufficient evidence to recommend any of these at present

Role of Physicians

- The physician should make themselves aware and adept at using technologies in diabetes with newer technologies and newer versions being constantly updated, the physician should guide the patient towards appropriate technology and digital solution selection.
- The physician should also be involved in training the patient in correct use of the tool/device, interpretation of reports through ongoing education and training.
- The physician should also make the patient aware of the limitations of technology and train to use conventional methods where needed.

Implementations

Almost ninety percent of the world's population is estimated to be within the reach of a mobile network[947] and the number of smartphone users also seems to be on the rise. Therefore, the feasibility of mobile apps to empower patients and healthcare providers is now a step higher than other approaches. Numerous mobile apps for diabetes management are nowadays available to help clinicians and/or the patients themselves to track and manage diet, physical activity, blood glucose targets, and medications Diabetes technologies are meant for saving time and better short-term and long-term outcomes. The choice should depend on the knowledge, infrastructure, and the need.

SPECIAL SITUATIONS

Post-Transplant Diabetes (PTDM)

RECOMMENDED CARE

- Pre-transplant assessment: History of diabetes, family history of diabetes, symptoms of microvascular and macrovascular complications, physical assessment including BMI, HBA1c, blood glucose monitoring as a part of pre-operative evaluation
- Perioperative hyperglycemia management as per in-hospital hyperglycemia protocol with insulin
- Treatment regimen upon discharge to be individualized based on the degree of hyperglycemia, comorbidities, and other factors
- For patients with hyperglycemia in the immediate post-operative period, regular monitoring of blood glucose on follow-up
- Individuals with pre-operative IGT or hyperglycemia in the perioperative period are at greater risk of PTDM and need close follow up
- Screening for risk factors of PTDM – modifiable, non-modifiable
- Assessment for PTDM to be done not earlier than six weeks after transplantation as per ADA criteria for DM (FBS, OGTT, HBA1c)
- For patients diagnosed to have PTDM, dietary advice and individualization of therapy – OADs or insulin
- Patients with PTDM are at greater risk for infections, transplant rejection, cardiovascular disease

LIMITED CARE

- Preoperative screening for diabetes/ IGT
- Perioperative blood glucose monitoring
- Reassessment at six weeks for PTDM
- Individualized treatment

Background

Post-transplant diabetes mellitus (PTDM) is the development of diabetes mellitus after solid organ transplantation. NODAT- New Onset Diabetes After Transplant, a frequently used terminology, may be misleading as individuals may have pre-existing IGT/DM, which gets discovered during the post-transplant period. PTDM is seen in 10-40% of transplants and has been known to increase the risk of infection and mortality rates. Timely evaluation and management of PTDM reduce morbidity, mortality, and transplant rejection rates.

Definition And Diagnosis Of New-Onset Diabetes After Transplantation

In 2003 the International Expert panel consisting of experts from fields of transplant medicine and diabetes suggested that the definition and diagnosis of diabetes and impaired glucose tolerance should be based on the definition and diagnosis described by the World Health Organization.[948] In 2011, the American Diabetes Association (ADA) incorporated hemoglobin A1C (A1C) > 6.5% as a diagnostic criterion for diabetes mellitus in the general population based on the observed association between A1C level and the risk for future development of retinopathy.[949] In 2014, the International Expert Panel recommended expanding screening tests for PTDM using postprandial glucose monitoring and A1C. However, because of potential confounding factors, the A1C test is not recommended early after transplantation (arbitrarily defined as within 45 days after transplantation).[950] A normal A1C does not exclude the diagnosis of PTDM in the presence of early post-transplant anaemia and/or dynamic kidney allograft function. The risk factors of PTDM are mentioned in Table 1.

Table 28. Risk factors for PTDM

Non-modifiable	Potentially modifiable	Modifiable
• African American, Hispanic • Age > 40–45 years • Recipient male gender • Family history of DM • HLA A30, B27, B42 • HLA mismatches • Acute rejection history • Deceased donor • Male donor • Polycystic kidneys	• HCV • CMV • Pre-transplant IFG/IGT • Proteinuria • Hypomagnesemia	➢ Individualization of Immunosuppressive therapy • Tacrolimus • Cyclosporin • Corticosteroid • mTOR inhibitors • Anti CD25 mAB ➢ Obesity or another component of the metabolic syndrome

Pathophysiology

The pathophysiology of PTDM involves increased insulin resistance and decreased insulin secretion. An immunosuppression regimen is one of the leading causes of PTDM, affecting insulin secretion and action.[951]

Detection Of PTDM

Pretransplant

In 2004 International Consensus Guidelines suggested that a pretransplant baseline evaluation should include a complete medical and family history, including documentation of glucose history.[952] Those with risk factors for metabolic syndrome can be screened further with laboratory testing.

After Transplant

The expert panel suggested that patients with early post-transplant hyperglycemia (defined as hyperglycemia 45 days after transplantation) should not be diagnosed as PTDM. New onset perioperative hyperglycemia is common and may be partly due to immunosuppressive therapy and stress hyperglycemia.[953]

Strategies For Prevention And Treatment Beyond Modification Of Immunosuppressive Regimens

Prevention

Pre-operative dietary and lifestyle modification is ideal for all potential transplant recipients regarding their risk of developing PTDM and may reduce the risk of patients with prediabetes developing PTDM. Sharif et al.[954] demonstrated the potential for benefit from lifestyle modification in kidney allograft recipients with impaired glucose tolerance.

Pharmacotherapy

Insulin: is the only safe and effective agent in the context of high glucocorticoid doses and acute illness early post-transplant. Still, the early and aggressive use of insulin may also have long-term benefits. In a randomized controlled trial, Hecking et al.[955] demonstrated the benefit of early basal insulin therapy following the detection of early posttransplant hyperglycemia (<3 weeks) at reducing subsequent odds of developing PTDM within the first-year post-transplantation by 73%. Although a relatively high glucose threshold of 200 mg/dL (evening or fasting) has been previously suggested, it may be reasonable to lower this threshold, but further research is warranted before firm guidance can be issued. The armamentarium of anti-diabetic therapy is increasing, and individual pharmacological risk/benefit profiles must be evaluated in the context of transplantation.[956–958] Further work to understand the pathophysiology underlying PTDM development and progression should assist the choice of pharmacological agents and form the basis of targeted clinical trials.

OADs: Werzowa et al.[959] in a randomized controlled trial, compared the safety and efficacy of vildagliptin (dipeptidyl peptidase-4 inhibitor) with pioglitazone (a thiazolidinedione) or placebo in kidney allograft recipients with impaired glucose tolerance. Adverse events were equivalent in all three arms, and pioglitazone and vildagliptin produced a comparable reduction in 2-h postprandial glucose levels. Metformin may be an attractive anti-hyperglycemic agent to reduce the likelihood of PTDM in high-risk individuals[960] benefits of metformin need to be weighed against the risks associated with metformin in the context of impaired renal function (e.g., lactic acidosis). However, this association has been the subject of critical analysis[961] and well-designed clinical trials are necessary to shed light on metformin's benefit versus risk ratio. Dose adjustments or cessation of oral anti-diabetic agents in renal allograft dysfunction should be individualized.

Modification Of Immunosuppression

Due to the lack of well-defined guidelines, modification of immunosuppression to alleviate the incidence of PTDM should be tailored to each patient. Reduction in immunosuppression should be weighed against the risk of acute rejection. The beneficial effect of steroid avoidance or withdrawal on the incidence of PTDM has been questioned by experts in the field because rapid steroid taper and the use of lower target cyclosporine and tacrolimus levels are now standard practice.[950]

In a meta-analysis of controlled clinical trials to assess the safety and efficacy of early steroid withdrawal or avoidance, Pascual *et al.* showed that steroid avoidance or steroid withdrawal after a few days reduced PTDM incidence among cyclosporine but not tacrolimus-treated kidney transplant recipients.[962] However, among cyclosporine-treated patients, acute rejection episodes were more frequently observed in steroid avoidance compared with conventional steroid-treated groups.[963] The use of tacrolimus and mTOR inhibitor combination therapy may increase PTDM risk and should probably be avoided. Nonetheless, a low dose calcineurin inhibitor (cyclosporine or tacrolimus) and mTOR inhibitor combination therapy seem justifiable in transplant recipients with a history of malignancies (such as skin cancers, renal cell carcinoma, or Kaposi sarcoma).

Deterrence And Patient Education

Pre-transplant patients should receive counseling regarding the risk factors of developing PTDM and how to prevent it. Attention to avoid weight gain is an established step to prevent PTDM. Weight loss can prevent PTDM in overweight patients with prediabetic status. In high-risk groups such as obese patients, the goal should include weight loss with diet, increasing physical activity with a target weight loss of 5% to 10% of total body weight, and following up with the dietitian before and after transplant. Patients should be advised to eat a healthy, low-calorie, low-fat diet. Weight loss immediately after transplant is not recommended, as it will delay wound healing.

After being diagnosed with PTDM, as with DM, self-glucose monitoring and compliance with treatment are essential. Also, patients should be aware of the importance of an annual eye exam, which is even more important than in traditional diabetes patients. PTDM patients are prone to the acceleration of cataracts due to the universal use of corticosteroids and immunosuppressants. Foot exams should be part of every clinical visit. Immunosuppressants place PTDM patients at increased risk of infections, so compliance with annual influenza and pneumococcal vaccines is critical in this population. Those patients who desire to get pregnant should be encouraged to wait at least one year after the transplantation to decrease the risk of rejection. The transplant team should be involved in all stages before, during, and after pregnancy to reduce the comorbidities of both mother and baby.[964,965]

Prognosis

PTDM decreases patient survival by increasing both cardiovascular events and the risk of infections. PTDM is associated with a higher prevalence of rejection and post-transplant renal failure. Studies showed that graft survival in patients with PTDM was 48% and 70% in patients without PTDM. Also, studies demonstrate that in kidney transplant recipients, cardiovascular events are 2 to 3-fold more in PTDM in comparison with other patients. Additionally, diabetic microvascular complications develop more rapidly in patients with PTDM than in traditional DM.[965–967]

Conclusion

PTDM is a common complication after solid organ transplantation and has been reported to be associated with increased morbidity and mortality. Risk stratification, intervention to minimize risk, and early diagnosis may alleviate the incidence of PTDM and improve outcomes following solid organ transplantation. Currently, early initiation of basal insulin therapy in patients with new onset hyperglycemia during the first post-transplantation week to preserve β-cell function and progression to overt PTDM cannot be routinely recommended. Management of established late PTDM should follow the conventional approach and guidelines established for the general population. Medical intervention is often necessary when lifestyle modification fails to achieve glycemic control. The choice of one antihyperglycemic agent over the other should be based on individual agents' potential advantages and disadvantages. Metformin appears safe in kidney transplant recipients with mild to moderate renal impairment (eGFR 30-60 mL/min). SGLT2 inhibitor has been suggested to be suitable for use following heart transplantation. Its use after kidney transplantation should be individualized. Similar to the general population, insulin therapy should be considered in individuals with suboptimal glycemic control despite multiple antihyperglycemic agent combination therapy.

DIABETES AND COVID-19

Recommendations

Recommended care

- All patients admitted with COVID-19 should be screened for hyperglycemia at admission.
- Screening for hyperglycemia at admission can be done with random capillary glucose obtained with a "reliable" glucometer, with values > 180 mg/dl inviting suspicion of hyperglycemia. This should be followed by documentation of glucometer-derived pre-meal and post-meal glucose values after the first significant meal during a hospital stay, with values of >140 mg/dl and >180, mg/dl respectively, suggestive of hyperglycemia.
- Continuous Glucose Monitoring systems (real-time) may be used as an alternative to glucometers to limit contact exposure to healthcare professionals
- Adoption of telemedicine practices should be encouraged for routine outpatient management of diabetic individuals with Covid19 infection.
- Patients without known diabetes who present with documented in-hospital new-onset hyperglycemia should be classified as having undiagnosed diabetes based on current HbA1c of ≥6.5%, while an HbA1c value of <6.5% should be classified as having stress hyperglycemia.
- We recommend that continued monitoring for hyperglycemia should be done with a standard glucometer daily in patients having hyperglycemia at presentation, including patients with
  - Fasting plasma glucose ≥ 110 mg/dl and/or HbA1c ≥ 6.5%
  - Pre-meal capillary BG ≥ 140 mg/dl
  - Post-meal/ Random capillary BG ≥ 180 mg/dl
- We also recommend that glucose monitoring should not be done once but continued during the course of the Covid19 illness, as these patients are at risk of hyperglycemia. Hyperglycemia may occur with clinical deterioration or institution of glucocorticoid therapy.
- We suggest initiating continuous intravenous insulin infusion in individuals with severe hyperglycemia (pre-meal glucose values of >300 mg/dl and/or post-meal values of >400 mg/dl) with simultaneous evaluation for ketosis.
- ACE-inhibitors and angiotensin receptor blockers can be safely continued as per general clinical indications.
- Outpatient contact should emphasize the importance of COVID-19 vaccination, including boosters, as per the national guidelines.
- Glycemic control and management of comorbidities should be optimized in all uninfected diabetic individuals as a primary prevention strategy.
- Post-covid reassessment of glycaemic status mandatory.
- Newly diagnosed diabetes to be treated according to standard diabetes protocol.
- Pre-existing T2DM to be screened and followed up, especially to detect complications.
- Stress hyperglycemia subjects to be educated regarding diabetes prevention strategies and re-evaluated on a regular basis to detect new-onset diabetes.

Limited care

- The principles are the same as recommended care and considerations for cost and availability of generic therapies.
- Venous samples for fasting plasma glucose and HbA1c should be sent after admission if laboratory facilities are available.
- In the absence of compelling indications for the use of insulin, we suggest that oral glucose-lowering agents can be continued in patients without any contraindications for oral antidiabetic drugs (OADs), such as in patients without renal/liver dysfunction, severe Covid19, ketoacidosis, severe hyperglycemia.
- In resource-constrained situations, sulfonylurea, metformin, or TZDs may also be used if there are no contraindications. Considering their relative safety, dipeptidyl peptidase- 4 (DPP-4) inhibitors can be continued.

Background

The Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has presented unprecedented challenges and tremendous strain on healthcare authorities. As of 3rd August 2022, there have been 575 million confirmed cases and 6.3 million deaths worldwide, with India reporting the second highest number of confirmed cases worldwide at 44 million and 0.5 million deaths.[968] Diabetes is one of the most common comorbidities in Covid19, with an estimated prevalence of 7-58%. The variable prevalence has been attributed to the age and gender proportions of the included patients in various studies, hospitalization status, and severity of illness, with higher prevalence noted in individuals with severe disease.[969,970] A bidirectional relationship between diabetes and Covid19 infection has become apparent since the beginning of the pandemic. Data from clinical studies have uniformly confirmed the poorer Covid19 outcomes in diabetic individuals, including increased risk of hospitalization, the severity of illness, intubation and ICU admission rates, and mortality.[971] The ambient hyperglycemia is postulated to increase viral replication in-vivo directly. Additionally, acute hyperglycemia can upregulate ACE-2 expression, increasing viral entry. Chronic hyperglycemia, on the other hand, decreases ACE-2 expression, shifting the balance towards a pro-inflammatory milieu. Diabetes is also characterized by compromised innate immunity and chronic low-grade underlying inflammation, which is heightened with an exaggerated release of pro-inflammatory cytokines like IL-6, potentially mediating the severity of Covid19 infection in diabetic individuals. Other non-hyperglycemia-related factors for adverse clinical outcomes include underlying comorbidities like hypertension, obesity, cardiovascular disease, and chronic kidney disease (CKD).[972,973] Conversely, Covid19 also has a deleterious effect on glycemic status. Exocrine pancreas and islet cells express ACE-2 receptors, which can mediate viral entry and direct pancreatic damage. This can clinically translate into exocrine pancreatic injury, including pancreatitis, in addition to worsening pre-existing hyperglycemia and new-onset hyperglycemia. Additionally, indirect mechanisms like overactivation of the renin-angiotensin-aldosterone (RAAS) system, corticosteroids, and cytokine release can contribute to impaired glycemic status. IL-6 is the primary cytokine culprit and can drive ketogenesis resulting in an increased risk of diabetic ketoacidosis.[974,975] Hence, the guidelines aim to highlight the importance of early detection of hyperglycemia and its attendant risks and propose treatment and follow-up algorithms to aid the management of diabetes in Covid19 patients. The guidelines also cover the management of hyperglycemia in these patients, which may be part of previously undiagnosed diabetes or transient hyperglycemia related to stress and other factors, including glucocorticoids.

Considerations

Timely diagnosis of hyperglycemia in Covid19 patients with or without diabetes and appropriate monitoring and management during hospital stay has important implications for morbidity and mortality. Guideline-recommended protocols can simplify the management of hyperglycemia for treating physicians both in-patient or in the outpatient setting.

Monitoring For Dysglycemia After The Acute Illness
Rationale and evidence

Primary prevention of infection in diabetic individuals

- Glycemic control and management of comorbidities should be optimized if not already appropriate with the ongoing medications.[972] The medications can be adjusted at the treating physician's discretion, with the primary target of optimizing overall glycemia as per targets recommended by general guidelines for diabetes. Previously held concerns about the role of ACE inhibitors and angiotensin receptor blockers (ARBs) in mediating adverse outcomes in COVID-19-infected patients have been largely mitigated. These medications can be safely continued as per clinical indications.[975]
- Telemedicine has flourished during the pandemic and has been a blessing in disguise. Most diabetic patients with Covid19 can benefit from remote consultations, and all attempts should be made to adopt telemedicine practices in outpatient care.
- Outpatient visits and consultations must be used to emphasize updated vaccination status, including booster/precaution doses as per the national guidelines.

Screening for hyperglycemia at presentation

- Plasma glucose at the time of hospitalization has been consistently demonstrated to be an independent predictor of adverse clinical outcomes. A recent meta-analysis confirmed blood glucose at admission as a significant predictor of mortality in diabetic patients with COVID-19, in addition to older age, male gender, insulin use, and presence of comorbidities like cardiovascular disease, CKD, and chronic obstructive pulmonary disease (COPD).[976] This was confirmed in a study by Kumar et al., where higher plasma glucose at admission strongly correlated with inflammatory markers, was predictive of moderate-to-severe disease, and patients with plasma glucose of 180 mg/dL or less had better survival.[977] In another recent meta-analysis, admission fasting blood glucose was found to be an independent predictor of disease severity, with every one mmol/L increase in fasting blood glucose translating into a 33% increased risk of disease severity.[978]
- Clinical guidance protocols have been previously published by Gupta et al. and the Ministry of Health and Family Welfare (MOHFW) for the management of diabetes in Covid19 infected patients.[979,980] We recommend that random glucose be obtained immediately at presentation in Covid19 infected patients, followed by documentation of pre-meal and post-meal glucose values after the first major meal post-admission. Venous samples for fasting plasma glucose can also be sent if laboratory facilities are available. This will aid in the early identification of hyperglycemia, timely management, and prognostication.
- Increased plasma glucose at admission can result from pre-existing uncontrolled diabetes mellitus, newly detected undiagnosed diabetes mellitus, the direct effect of the virus on pancreatic β cells, or stress/drug-induced hyperglycemia. New-onset hyperglycemia was noted in as many as 10.3% of patients without known pre-existing diabetes at admission in the study by Kumar et al.[977]
- The PISA COVID-19 study revealed that patients with new-onset hyperglycemia had the highest mortality, twice that of normoglycemic patients, and 30% higher than patients with pre-existing diabetes mellitus.[981] Similar findings of worse outcomes in new-onset hyperglycemia compared to pre-existing DM have been demonstrated in other studies.[982–984] This might be secondary to occult end-organ damage in undiagnosed diabetic individuals or insulin secretory defects and increased insulin resistance resulting from a severe infection leading to pancreatic β-cell destruction, a more severe inflammatory state, and corticosteroid use. Conversely, it can be argued that known diabetic individuals tend to have better control of hyperglycemia and comorbidities. This is supported by the fact that diabetics with optimal glycemic control have better outcomes than patients with poor control.[985]
- Venous samples for HbA1c should be sent on admission at centers where such laboratory facilities are available. Patients can be categorized as "pre-existing DM" if known as diabetic or on anti-diabetic agents. Other patients with hyperglycemia can be categorized as "undiagnosed DM" if HbA1c ≥6.5% and "stress-induced hyperglycemia" if HbA1c <6.5%.

Continued monitoring for hyperglycemia during the hospital stay

- Hyperglycemia after admission and hypoglycemia have been demonstrated to be associated with poorer outcomes in Covid19.[986] Hence, we recommend that continued monitoring for hyperglycemia should be done daily in patients with hyperglycemia at presentation, in concordance with the MOHFW guidelines.[979] This would include patients with
  - Fasting plasma glucose ≥110 mg/dl and/or HbA1c ≥6.5%
  - Pre-meal capillary BG ≥140 mg/dl
  - Post-meal/ Random capillary BG ≥180 mg/dl
- Additionally, hyperglycemia can develop during the course of Covid19 illness, especially with clinical deterioration and corticosteroids. Hence, we recommend continued monitoring of blood glucose daily in these admitted patients as well.
- Glycemic monitoring should be performed with a reliable glucometer, the frequency depending upon the treatment chosen for hyperglycemia management. Capillary blood glucose values should be interpreted cautiously in sick patients with hypoxia and hypoperfusion.
- Continuous glucose monitoring (CGM) real-time devices may be used as an alternative to glucometers to limit contact exposure to healthcare professionals. This would provide glucose values for timely adjustment of medications, including insulin, alert for extremes of blood glucose values, and minimize close contact between health care providers and the patient during capillary glucose monitoring. CGM devices which require autocalibration / no calibration with capillary BG values may be preferable in this scenario. CGM has demonstrated reliability and utility in critically ill Covid19 patients on intravenous insulin infusion in a few studies.[987,988] However, CGM devices are not widely available owing to cost concerns, with many medical professionals not well-versed with the meaningful interpretation of CGM data. It is recommended that physicians get familiar with newer technologies like CGM and get adequately trained to manage diabetic patients using CGM-derived metrics and graphs. Limitations of CGM include a small-time lag between blood glucose and interstitial glucose, limited utility in the presence of hypoxemia, hypoperfusion, and rapidly fluctuating values, and a wider coefficient of variation at extremes of blood glucose values. We recommend the following CGM-based glycaemic targets: -
  - Time-in-range, TIR (70-180 mg/dl): >70% (>50% in elderly individuals)
  - Time-below-range, TBR (<70 mg/dl): <4% (<1% in elderly individuals)
- Inpatient glycemic control is vital for better long-term outcomes in Covid19 infected patients. In a study from China, T2DM patients with well-controlled blood glucose between 70-180 mg/dl during the hospital stay had markedly lower mortality.[989] This was similar to the results observed in the study from India by Kumar et al., where higher mortality was seen in Covid19 patients with BG >180 mg/dl on admission.[977] Similarly, inpatient BG values of >180 mg/dl were associated with a longer median length of stay and higher mortality in the study by Bode et al. [990]
- We agree with the MOHFW guidelines (12) concerning capillary BG targets and recommend the following glycemic targets
  - Patients on basal-bolus regimen: Premeal BG < 140 mg/dl, post-meal BG <180 mg/dl
  - Patients on intravenous insulin infusion: Target range of 140-180 mg/dl

Implementation

Standard protocols, as recommended here and in other society guidelines must be widely disseminated among practicing physicians for quality care. We would like to re-emphasize the importance of screening for hyperglycemia at initial presentation and the continuation of glucose monitoring in high-risk individuals. The choice of therapy should be based on the patient's clinical condition, comorbidities, any contraindications to specific medications, and severity of hyperglycemia. The goal is to achieve the recommended glycemic targets for better clinical outcomes. All normoglycemic discharged patients should be followed up for new-onset hyperglycemia. If normoglycemic, further screening should be based on the prevalent screening recommendations.

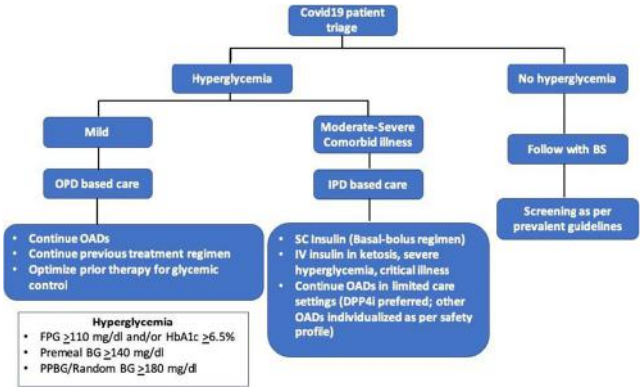


Figure 17: Approach to management of hyperglycemia in patient with Covid19

Travel and Diabetes Recommendations

Recommended care
• Preparation of pre-travel arrangements and specialized guidance for the vacation under the treating physician is appropriate to start at least a month prior to the date of journey. • Comprehensive discussion with the treating physician about the destination place, mode of traveling, activity level, and socio-environmental detailing are of utmost need. • Individuals must carry a physician's advice along with a list of all medications with a generic name and their dosages in a separate, easily accessible container. • Travel Health insurance is a must, and patients should be immunized with vaccine-preventable diseases concerning the destination. • Airport security requiring patients going through body scanners should be careful as pumps and CGM may undergo radiation-induced malfunction. • In air travel, patients should carry medicines and carbohydrate-rich snacks in their luggage. • In air travel, patients should not inject insulin or use a pump at take-off or landing due to pressure differences which may lead to irregular in insulin administration. • Traveling across more than five time zones requires insulin dose and frequency adjustment. • In air travel, there is an increased risk of developing deep venous thrombosis (DVT), which can be easily prevented by simple recommended maneuvers and hydration. • Train travel is more flexible, health insurance is not necessary, but snacks and medications should be carried in easily accessible bags. • During travel, there will be an inadvertent change in activities, and hence, medications should be adjusted and blood sugar levels should be checked regularly.

Limited care
• It is essential to procure a prescription/ recommendation letter from the physician describing the patient's medical condition, and their current diabetes medication regimen. • It is prudent to advise the patients to plan for travel delays and lost luggage, so taking twice as many diabetes supplies and medications is recommended, preferably distributed in different luggage bags. • Food options for diabetics may be limited during travel and travel planning should offer greater flexibility in dietary choices. • Use of the correct syringes with specific insulin concentrations is essential as insulin formulation varies in different countries.

Background

Travelling is defined as an individual's exposure to unfamiliar socio-environmental places, irrespective of the purpose. Those with chronic illnesses, like diabetes, may be vulnerable to the emotional and physical stresses associated with traveling. However, when unfamiliar foods, unaccustomed climate, different time zones, and social conditions are considered during times of travel, patients may face challenges in managing their diabetes .[991] A study conducted in Aberdeen, UK, showed that 15% of insulin users stated that their use of insulin affected their choice of travel destination, both in terms of health risk in developing countries and avoidance of long-haul travel.[992] However, individuals with diabetes can travel safely with adequate preparation and appropriate self-management skills.

Pre-Travel Recommendation

Visit treating Health Care Professionals (HCP)

Patients with diabetes planning to travel should schedule an appointment with their treating physician at least a month in advance of their trip to allow for planning of diabetes care when traveling. This will also enable an updated assessment of glycemic control, evaluation and review of travel risks, and a discussion of the patient to minimize these risks. In addition, the physician can remind the patient and reiterate some important self-management principles, e.g., recognition and treatment of hypoglycemia symptoms, sick day guidelines, and self-monitoring of blood glucose requirements. It is important to procure a prescription/letter from the physician describing the patient's medical condition, their current diabetes medication regimen, and the patient's medical necessity to carry sharps, e.g., needles and lancets, if the patient is on an insulin regime.[993,994] It is prudent to advise the patients to plan for travel delays and lost luggage, so taking twice as many diabetes supplies and medications is recommended, preferably dis tributed in different luggage bags.

Those planning to travel should schedule an appointment with their treating physician, at least a month in advance of their trip for an updated assessment of glycemic control and should also procure a prescription describing the patient's medical condition, and medication. A diabetic individual should also carry an extra number of medicines that are distributed properly.

Know your destination

It is of utmost importance to find information regarding the climate and environmental conditions of the destination. Extremes of weather can adversely affect the health of the patient and/or degrade medications, supplies, and equipment [995,996]. Patients with diabetes are more susceptible to environmental stressors than their counterparts. Patients taking insulin or other injectable medications that are temperature sensitive should investigate the availability of refrigeration, e.g., refrigerators in hotel rooms and travel cold packs, at their destination and plan if such facilities do not exist, i.e., travel cold packs can be packed prior to departure. Suitable clothing should be carried based on the climate at the destination. Protective gear such as hats/sunglasses/sunscreen, gloves/mittens/boots, and comfortable footwear will enable patients with diabetes to enjoy their trip without putting themselves at higher risk for heat exhaustion, cold exposure, or foot ulcers.[997]

Information regarding the climate and environmental conditions of the destination is a must. Extremes of weather can adversely affect the health of the patient and/or degrade medications, supplies, and equipment. Patients with diabetes are more susceptible to environmental stressors than their counterparts, such as increased incidence of heat exhaustion, cold exposure, or foot ulcers.

Diet

Food options for patients with diabetes may be limited during travel, especially if one is traveling out of the country, so planning is important.

This is more relevant during air travel, as travel by road/train and maritime travel offer greater flexibility in dietary choices.[998] For flights during which a meal will be served, there is an option of selecting your choice of meal well in advance. The destination and flight duration are also important with regard to the food options available. Packing healthy snacks in carry-on luggage can take care of disrupted dietary patterns during the flight. Access to such foods may be limited during travel, and it is recommended to be carried to help prevent or treat hypoglycemic events. When traveling to countries where English is not the primary language, food labels and restaurant menus may be difficult to interpret. In such situations, investigating specific dietary options before departure via the internet, may be helpful. When unsure, it is best to rely on known low-carbohydrate options, e.g., salads, nuts, and eggs.[999]

Food options for diabetics may be limited during travel and travel planning should offer greater flexibility in dietary choices; packing healthy snacks in carry-on luggage can take care of disrupted dietary patterns.

Medication

For insulin users, it is important to note that insulin concentration varies in various countries. Available options include U-40, U-100, or U-200. The use of the correct syringes with specific insulin con centrations is essential, since using wrong syringes may deliver incorrect dose of insulin. This concern is dimin ished in those who use insulin pens rather than vial and syringes. It is also important to note that the unit of blood glucose measurement in India is mg/dL, but many other countries use mmol/L. This will be important if someone's glucose meter malfunctions while abroad and another one needs to be bought locally. Travelers should be also aware that not all insulins, other injectables, or oral diabetes medications available in India will be available in every country throughout the world and that different names may refer to medications.[1000] Therefore, it is important to carry a list of all medications with generic name and their dosages. Those who are on insulin pump therapy should contact the manufacturing company for contact details at the destination, should there be a need. They must discuss with their treating physician about an alternative basal-bolus insulin regimen in the event of pump failure. Immunization against common and travel-related vaccine-preventable diseases is recommended, as per individual country recommendations, prior to departure.

It is advisable to disconnect the pump during take- off or landing as change in cabin pressure may lead to excess insulin delivery. Insulin concentration varies in various countries; hence, using the correct syringes is essential. Unit of blood glucose measurement may also be different. Availability of medications may also be an issue. So, it is important to carry a list of all medications with generic name and their dosages. Immunization against common and travel-related vaccine--preventable diseases is recommended. Those on insulin pump therapy should get in touch with the manufacturing company and it is advisable to disconnect the pump during take off or landing as change in cabin pressure may lead to excess insulin delivery.

Travel health insurance

Where feasible, travellers need to get in touch with their medical insurance companies and review their medical coverage policies during travel should unforeseen emergencies arise. One should have easy access to their health insurance identification card. It is also important to locate the nearest hospital and phar macy at the destination, before arrival, in case medical assistance is required. It would be wise to ensure that health insurance is accepted at these facilities beforehand to avoid expensive medical bills or unforeseen costs.

Individuals with diabetes should also carry travel health insurance.

What To Pack

Physician prescription

1. Letter should be in English.
2. Whether the patient has type 1 or 2 diabetes.
3. Medications (generic name) and dosages—if on insulin pump, settings and basal-bolus backup regimen, in case of pump malfunction, should be included.
4. Rescue medications, viz glucose gel, tablets, and a gluca gon pen.
5. Supplies with quantities mentioned (glucometer, testing strips, lancets, syringes/pens, and batteries).
6. Necessity to carry sharps (needles and lancets).
7. Physician name and contact details.

Always keep double medicines and supplies than needed for travel. Do not pack them all in one place. Keep half the supplies in a bag that will be with the concerned individual in person, irrespective of the mode of travel.

- Health insurance policy/card or details
- Diabetes medications and prescriptions for them
- Rescue medications (glucose gel, tablets, and glucagon pen)
- Supplies (syringes, lancets, test strips, sharps container)
- Two glucose meters (in case one fails) with extra batteries
- If on insulin pump, twice as many pump supplies as may be needed
- Coolant/cold packs/insulin wallets for insulin users
- First aid kit
- Comfortable shoes
- Protective clothing, depending on destination climate
- Some snacks to avoid hypoglycemia

One must carry physician's prescription, health insurance policy, medications and prescriptions for them, rescue medications, snacks, supplies, glucometers, coolants, pumps in double, a first aid kit, comfortable shoes, and protective clothing.

Air Travel

Airport security

Travel security, both national and international, has become strict in recent years. When traveling by air, outside the country, passengers should contact the airline to find out if the destination country has any specific airport security restrictions or requirements regarding diabetes medications or equipment. If a traveller is on an insulin pump or a continuous glucose monitor (CGM), it is important to ensure that the device not be removed since it is attached via a catheter underneath the skin. It is also prudent to check with the pump CGM manufacturing companies regarding recommendations for radiation exposure. Several companies allow the pas sage of their equipment through metal detectors but do not recommend that their products be run through the x-ray machines or body scanners that implement x-ray technology, due to the potential risk of radiation-induced malfunction. This information may be available online and can be printed and shown to security personnel.

Airport security requiring patients on pump or CGM to go through scanners should be warned from doing so as it may cause radiation-induced malfunction. These devices should not be removed also.

Storing diabetes medications and supplies

Carrying snacks that contain carbohydrates is a good backup in addition to glucose tabs, gels, or glucagon kits, in case blood sugars fall low. Having diabetes supplies in carry-on luggage is also beneficial. Temperature extremes occur more frequently in the lug gage compartments than in the cabin areas on airplanes, which is important to consider when carrying insulin vials or

pens. Injectable diabetes medications have optimal storage temperatures between 2 and 8 °C while oral medications can be stored between 20 and 30 °C.[1001] Insulin pumps have temperature tolerances of 5–40 °C and CGM devices from 10 to 40 °C; but specific temperature ranges vary by manufacturer. Blood glucose testing strips should be kept in tightly sealed containers to avoid exposure to moisture. Do not expose them to extreme temperatures. Travelers should read the package inserts of their medi cations, devices, and equipment to ensure proper functioning. In India, very recent Clinicare (India) Pvt. Ltd., a Mumbai-based company, has launched the FRIO ® Insulin Wallet. This is meant for keeping insulin cool while traveling and is a good option when one has no access to refrigeration or during power shortages while traveling. Unlike traditional insulin-carrying cases, FRIO®'s cooling properties are not derived from an ice pack or anything that needs refrigeration. It is easily activated by water. It is an environment-friendly green reusable product and is convenient to be carried around on oneself or in one's hand baggage.[1002]

Air travel requires patients to carry carbohydrate snacks, insulin, insulin pump, and medications in carry-on baggages to maintain temperature stability.

Insulin on board

Depending on the duration of the flight, insulin may need to be administered on board an airplane. Due to pressure differences in the cabin area, resistance may arise when using syringe plungers to draw insulin.[1003] Similarly, with insulin pen devices, there may be a leak in insulin when applying the pen tip needle for use. Recent data suggests the possibility of unintended insulin delivery during ascent from bubbles precipitating out of insulin solution in the microtubules according to pressure gradients for those using insulin pump therapy on board an aircraft.[1004] In addition, there have been reports of significant unintended insulin administration due to plunger movements during rapid cabin depressurization during an emergency. More data is needed before recommendations regarding insulin pump management during flight can be made.[1005] Travelers must check their blood sugars frequently due to the effects that stress, altered eating habits, and altered medication administration times may have on overall blood glucose control.

Due to pressure differences in the cabin area, there might be some irregularities in insulin administration. Even in insulin pumps, similar issues may arise due to bubbles precipitating out of insulin solution in the microtubules. Blood sugars must be frequently checked.

Traveling across time zones

Diabetes management is based on a 24-h cycle. When traveling from west to east, one should remember that the day shortens compared with when traveling from east to west, when the days become longer .[1006] Usually, if fewer than five time zones are crossed dur ing travel, adjustments to insulin dosing are generally not necessary.[1007] If more than five time zones are crossed, the treating physician should make specific recommendations to discuss how insulin dosing or timing of administration should change based on time zone differences. For those on oral medications, timing is less important. Patients should be educated not to take their sulfonylurea if they will be missing meals during travel to avoid hypogly cemia. However, other oral agents may be continued. Generally, it is helpful if travelers keep their wristwatch set to their departure time zone, at least for the first day of travel..

Traveling across less than five time zones does not require insulin dose adjustments, but in greater than five time zones, dose and timings need to be adjusted.

Prevention of venous thromboembolism in air travellers

Those with diabetes may be at an increased risk of developing deep venous thrombosis (DVT).[1008,1009] Therefore, they should be encouraged to stand and walk during long flights every 1–2 h while awake and perform seated dorsiflexion/plantarflexion exercises to avoid venous stasis that could potentiate clot formation. Staying well hydrated throughout the flight may also decrease the risk of DVT formation.

Those with diabetes are at an increased risk of developing deep venous thrombosis, so they should be encouraged to stand and walk during long flights every 1–2 h and perform seated dorsiflexion/plantarflexion exercises to avoid venous stasis; also, one must remain well hydrated.

Train travel/road travel

In general, traveling by train and/or road is a much more flexible option for a person with diabetes, especially concerning diet and medications. However, it is mandatory to have a visit with the HCP pretravel, and it is most definitely beneficial to know details about the destination. Since train/road travel is feasible only within the country, specific travel health insurance is not a pre-requisite. Still, it would be helpful to review one's medical coverage policies and get a list of hospitals/clinics wherein their current insurance will be accepted, at the destination, should unforeseen emergencies arise. The list of what to pack remains the same, as above. For carrying and storage of insulin, as mentioned above, FRIO® Insulin Wallet may be a good option.[1002]

Train travel is much more flexible; though health insurance is not required, one must pack the same essentials in carry-on bags.

Recommendations After Arriving At The Travel Destination

Physical activity

Depending on travel itineraries, there may be an inadvertent increase in walking more than one is accustomed to (whether at their destinations or in airports between security and boarding gates). This increase in physical exercise may increase glucose utilization and lower blood sugars in addition to more rapid insulin absorption. In such a situation, it may be useful to slightly decrease the insulin dosages or eat more carbohydrates and snack between meals to keep blood glucose levels controlled appropriately.[1010] It is also advisable to check blood sugar levels more frequently, to be able to keep a track on overall glycemic control. This is considering exposure to a new cuisine, a new environment, and a potentially different physical activity levels.[1003] With increased walking comes the need for comfortable footwear since blisters and abrasions can develop from improperly fitted shoes. Wearing sandals on beaches to reduce the introduction of bacteria and other stray ob jects is advisable.[1011]

During travel, there will be an inadvertent increase in walking, for which insulin requirement will decrease; frequent snacking may also help. Blood sugar must be measured more frequently.

One must wear proper footwear to avoid ulcers and infections.

Keeping hydrated

It is important to remain hydrated, especially when traveling to hotter climates. It is also important to know the quality of the potable water available at one's destina tion to avoid traveler's diarrhea and the ensuing dehydra tion.[1012,1013]

Conclusion

Travelers with diabetes can face challenges during their trips, particularly international travelers. In general, traveling within the country in the same time zone, be it by air or train, poses less of a challenge than traveling outside the country to a destination with a different time zone. Being prepared by planning, in advance, will be helpful to achieve management of diabetes and boost self-confidence. This is of utmost importance to achieve appropriate patient glucose control amidst changing diet, time zone difference, and a new environment. Patients should meet their

treating physician at least 1 month prior to travel, to allow time for the physician to generate a travel letter and/or prescriptions for needed medications, equipment, and supplies. Diabetes is manageable when patients and their providers work together to formulate a treatment plan for travel. No destinations should seem "off-limits" to individuals with diabetes, given the available resources to be utilized in preparation for travel. It is always advisable to take extra precautions while traveling to high altitudes (above 8000 ft.) as low oxygen level there may offset glycemic control. While the above guidelines outlined here seem reasonable, there is no information on how many patients actually have any knowledge of the basics or seek pretravel counseling, and the area remains largely understudied. More data on the diabetic traveling population is needed so that better evidence- based guidelines can be developed.

Tips For Safe Trips

1. Plan your tour well in advance. Consult your physician and discuss it in detail about tour schedule.
2. Carry the prescription, important documents, and a list of all the supplies at hand.
3. Always carry insulin/medicines/accessories double your required amount.
4. Use comfortable shoes; always carry some snacks/ glucose tabs or gel while on the move.
5. Remain hydrated, avoid unaccustomed food and physical activities, and avoid alcohol in excess.
6. Always take help from co-travelers or travel agents in an emergency.

Steroid-induced hyperglycemia

Recommendations

Recommended care[1014,1015]

• Consider screening for glucocorticoid-induced diabetes should be in all those treated with medium to high doses of glucocorticoids.

• **If there is no previous diagnosis of diabetes**

◦ Prior to the commencement of steroids, check Hb1Ac in individuals perceived to be at high risk.

◦ Once steroid initiated, recommend capillary blood glucose (CBG) once daily. It should be done pre or post-lunch or evening meal, in those at high risk or with symptoms suggestive of "hyperglycemia".

◦ If CBG is below 216mg/dl, we consider it at low risk and then record the capillary blood glucose daily post breakfast or post-lunch

◦ There is no need for capillary blood testing if the value is consistently less than 180 mg/dl.

◦ Increase the testing frequency to four times a day if the value of capillary blood is found more than 216 mg/dl.

◦ Consider treatment initiation if capillary blood glucose is found to be consistently greater than 216 mg/dl (i.e., on 2 occasions during a 24-hr period)

◦ Suh et al. recommend initiating therapy when pre- or post-prandial glucose repeatedly exceeds 140 mg/dL or 200 mg/dL respectively

• *If the patient is a known diagnosis of diabetes*

Review glucose control and current therapy.

We must set a target of blood glucose in the range of 106-180 mg/dl. (Acceptable range 106-216 mg/dl**)**

Start checking capillary blood glucose four times a day and accordingly adjust diabetes medications

Resource limited considerations

• If blood glucose remains stable for over 24 hours, monitoring can be reduced to 3-4 hourly intervals in appropriate cases.

• If the patient is on parenteral feed, glucose monitoring every 4 to 6 hours is recommended.

• Blood glucose monitoring should be more frequent (30 min to every 2 hours) if the patient is receiving IV insulin.

• Furthermore, if the patient is receiving intravenous insulin, blood glucose monitoring should be more frequent, ranging from 30 minutes to every 2 hours.

Therapeutic goals

• There is no clear evidence for establishing therapeutic goals for patients with SIHG.

• American Diabetes Association (ADA) glucose targets for patients with SIHG are not from those with any other type of diabetes.[1016] It should be individualized according to life expectancy, comorbidities, patient compliance, and risk of hypoglycemia.

• In hospitalized patients: a Target glucose range of 140–180 mg/dL is recommended for most critically and non-critically ill patients.

• More stringent goals: 110–140 mg/dL. It may be appropriate for selected patients if this goal can be achieved without relevant hypoglycemia.

• **In People with COVID-19**: < 180 mg/dl[1017]

Frailty: 120 –200 mg/dl throughout the day[1018]

Care home residents: 126-216 mg/dl

End of life care :106- 270mg/dl

• Large blood sugar fluctuations can occur with the use of steroids if the patient suffers from:

◦ Severe underlying disease (e.g., cancer),

◦ In the perioperative care setting (e.g., recently transplanted patients or those requiring steroids as supportive therapy

◦ Those who receive concomitant complex therapies (chemotherapy, immunosuppressants, etc.)

Background

Glucocorticoids increase insulin resistance, leading to hyperglycemia, in diabetic and non-diabetic patients. Steroids are used for their anti-inflammatory property to treat a variety of conditions in both inpatient and outpatient settings. It is challenging to manage steroid-induced hyperglycemia (SIHG) as there are no clear recommendations from various societies due to the paucity of data.

SIHG is defined as abnormally elevated blood glucose associated with the use of glucocorticoids in patients with or without pre-existing diabetes mellitus. Oral glucocorticoid use is linked to 2% of cases of new-onset diabetes mellitus globally in a 2006 study.[1019] The prevalence of steroid use in people with diabetes in hospital in-patients varies between 25-40% of the population.[1020] The diagnostic criteria for SIHG are the same as in other types of diabetes, but diagnosis is reasonably challenging in patients with SIHG. One important reason is as fasting blood glucose might be normal if short- or intermediate-acting glucocorticoids are administered in single morning doses. If an oral glucose tolerance test is performed in the morning hyperglycemia might be absent after glucose exposure as the diabetogenic effect of the glucocorticoids is not yet present. In those with new-onset glucocorticoid therapy, HbA1c might be inconspicuous. It is possible that diabetes can persist and glucocorticoids just unmasked a pre-existing glucose metabolism disorder.[1021] Acute illness may result in "stress hyperglycemia" independent of steroid administration.[1022] Apart from activating anti-inflammatory proteins and repressing pro-inflammatory proteins, steroid administration modulates carbohydrate metabolism. It is via complex mechanisms, including effects on beta cell function as well as inducing insulin resistance.[1023]

Management

• Usually, SIHG cases are managed as per strategies to lower glucose in patients with T2DM.

• Intensification of anti-hyperglycemic therapy should be done

• Re-evaluation of SIHG cases should be performed

• The glucose-lowering agents of choice should match daily glucose profiles.

• Consider the mechanism of action of glucocorticoid agents to select anti-hyperglycemic therapy.

• We don't have enough evidence for the clinical efficacy of using OHA for in-hospital SIHG cases.

When to use OHA

• In patients with the stable, non-critical disease and mild hyperglycemic excursions, OHAs might be an adequate choice.

Choice of antidiabetic[1024–1027]

Table 29: Choices of antidiabetics

Metformin	• It enhances insulin sensitivity and reduces insulin resistance. • It can be continued in pre-existing T2DM unless contraindications exist. • The effectiveness of metformin to counterbalance glucocorticoid treatment is fairly scarce.
Pioglitazone	• It enhances insulin sensitivity and reduces insulin resistance. • It can be continued in pre-existing T2DM unless contraindications exist.
Insulin secretagogues	• It stimulates endogenous insulin production • It might be suitable to tackle mild SIHG in the inpatient setting, specifically in inpatients who are non-severely ill and
	who receive short-acting steroids once daily in the morning • Use insulin & Sulphonylureas with caution as there is an increased risk of hypoglycemia. When steroid doses are tapered or meals are skipped be careful about hypoglycemia
DPP4-Inhibitors	• The side effect profile of DPP4 inhibitors is safe. • So, it might support their use in hospitalized patients with SIHG.
SGLT2-Inhibitors	The use of SGLT2 inhibitor has shown to be safe in patients hospitalized for COPD developing SIHG. Its use has not been found to improve glycaemic control or clinical outcomes.
GLP-1 Ras	• Its use is associated with the risk of gastrointestinal adverse effects, particularly during the initiation phase. • It limits their broad usage for acutely ill, hospitalized patients with SIHG.
α-Glucosidase inhibitors (AGIs)	One study found the combination of glinides and AGIs improved glucocorticoid-medicated postprandial hyperglycemia in patients with rheumatoid arthritis
Insulin	• Use insulin for outpatients treated with long-term, once-daily glucocorticoids and for whom only postprandial glucose is elevated. • In such cases, neutral protamine Hagedorn (NPH) insulin is a preferable option. • It can be administered at the same time when glucocorticoid in the morning is given. • It has a closely aligned temporal profile (peak 4–10 h, duration of action ≥14 h) with the hyperglycemic excursion induced by intermediate-acting glucocorticoids. • When twice-daily intermediate-acting or long-acting glucocorticoids are
	administered, the total dose of NPH insulin can be divided or substituted for long-acting basal insulin (insulin detemir or glargine).

Patients with significant hyperglycemia and severe illness[1028–1030]

Insulin remains the treatment of choice in the hospital setting. The insulin therapy chosen for SIHG must take into account the user agent, the current dose, the time point, and the interval of the glucocorticoid administration into account. It is a good practice that in patients with pre-existing T2DM already requiring insulin, a 20% increment in daily insulin dose is required upon the addition of glucocorticoid therapy to achieve similar glycaemic control. Oral hypoglycemic agents can be added to insulin therapy when patients continue to exhibit severe or persistent hyperglycemia (HbA_{1c} >9%). In patients with severe or persistent hyperglycemia to high glucocorticoid doses, multiple daily or long-acting glucocorticoid use, basal-bolus insulin should be initiated. These regimens offer great flexibility in dose titration.

Patients Already On Insulin

Patient on short-acting insulin

If hydrocortisone is used, the expectable glucose profile will likely show a fast and robust increase in sugar but only for a short duration. These transient and self-limiting glucose peaks require glucose-lowering therapy on a case-to-case basis. The agent of choice in such a scenario is short-acting insulin (rapid-acting insulin analogs or regular insulin). It should be injected at the time or shortly after glucocorticoid administration. Recommended Initiation of the dose is 0.1 IU/kilogram (kg) bodyweight (BW). Insulin therapy can be intensified by schematic increments of 0.04 IU/kg for pre-prandial values from 200–300 mg/dL or 0.08 IU/kg for values ≥300 mg/dL as insulin requirements are glucocorticoid dose-dependent, reduction of glucocorticoid is usually related to an improvement of glycemia. Reduction of rapid-acting insulin should be performed proportionally to a decrease in glucocorticoid dose.

Patients on intermediate-acting insulin

Intermediate-acting glucocorticoids such as prednisolone and methylprednisolone are the most commonly prescribed steroid agents. Having high glucocorticoid activity makes them useful for long-term anti-inflammatory and immunosuppressant treatment. With a single dose administration in the morning, hyperglycemia develops slowly, but continuously. It lasts until the evening and gradually recovers until the next morning simultaneously following the peak and duration of action of the steroid agent. This pattern is suitable for short- or intermediate-acting basal insulins such as insulin detemir or NPH (neutral protamine Hagedorn). A clinical recommendation to initiate insulin with a dose of 0.4 IU/kg of NPH insulin is warranted. If the patient is on multiple daily administrations of intermediate-acting glucocorticoids, hyperglycemia might overlap and persistent hyperglycemia can occur. In this scenario, NPH insulin once daily will not be sufficient. Switch to NPH twice daily or switch to longer-acting insulin (e.g., glargine). If necessary, add rapid-acting insulin boluses.

Patients on long-acting insulin[1031,1032]

Dexamethasone has a prolonged duration of action lasting for more than 24 h. Hyperglycaemia in association with long-acting glucocorticoids, develops slowly, peaks during the day (varying time points) and is sustained for 24 h after intake. Generally, intermediate-acting basal insulins (NPH insulin, insulin detemir) should be prescribed twice daily (an initial dose of 0.3 IU/kg BW). Alternatively, long- or ultralong-acting basal insulin analogs (insulin glargine U100/U300 or insulin degludec) might be the most appropriate insulin to control hyperglycemia in this situation (initial dose 0.2 IU/kg BW). No data exists for new generation ultra-long-acting basal insulin analogs for the treatment of SIHG. In the recent COVID-19 pandemic, dexamethasone use was justified in the appropriate situation.

Covid, Steroids, And Hyperglycemia

In insulin-naïve patients
• Start NPH insulin when glucose exceeds a threshold of 216 mg/dL in a dose of 0.3 IU/kg/day while 2/3 should be administered in the morning and the remaining third in the evening.
• A dose reduction to 0.15 IU/kg in case of age >70 years or eGFR below 30 mL/min has been proposed.
• Titrate according to morning or evening glucose values in a manner of a reduction of 20% if the glucose falls below 70 mg/dL or decreased by 10% in case of glucose between 70–110 mg/dL.
• Insulin dose should be up-titrated by 20% if glucose values exceed 320 mg/dL and by 10% if glucose values are between 220–320 mg/dL.

After Discharge

Tapering is not required if steroids have been used for short duration.[1033] After steroid therapy, monitoring of blood sugar is continuously warranted as we anticipate pre-steroid blood glucose levels after stopping anti-hyperglycaemic medications. Test Hb1Ac after 3 months post steroid therapy.

Diabetes And Pregnancy

- Steroid administration in pregnancy may cause transient hyperglycemia or result in increased levels of hyperglycemia in those with gestational diabetes mellitus or pre-existent diabetes.
- If blood glucose readings remain high, this can have adverse outcomes for the mother and fetus, and this is true for women with pre-existing diabetes and gestational diabetes.
- The majority of steroid use in pregnancy will be two single doses of betamethasone administered intramuscularly to promote fetal lung maturity at birth.
- Various strategies have been used to manage significantly raised blood glucose in women given betamethasone, and these include the use of a variable rate intravenous insulin infusion, continual insulin systems (CSII), or titration of existing insulin regimens.
- There is no clear evidence as to which method is the most effective.

Table 30: Different corticosteroids and their equivalent doses, steroidal kinetics and potential to trigger hyperglycemia.

Glucocorticoids	Peak concentration (minutes)	Equivalent dose (Approx.)	Half-Life (Hrs)	Duration Of action (Hrs)	Hyperglycaemic Effects (Hours)		
					Onset	Peak	Resolution
Hydrocortisone (Short acting)	20	10	2	08-Dec	1	3	6
Prednisolone Methylprednisolone (Intermediate acting)	5 4	60-180 60	2.5 2.5	12-36 12-36	4 4	8 8	12-16 12-36
Dexamethasone (Long acting)	0.75	60-120	4	36-72	8	Variable	24-36

Recommended Care

- Conduct preoperative assessments: baseline history of diabetes, assessment of microvascular and macrovascular complications, HbA1c, serum electrolytes and creatinine level, and current treatment regimen.
- Maintain serum glucose of 140-180 mg/dL for all in-hospital patients (ICU and for general care medical and surgical wards).
- Sulfonylureas, meglitinides, TZDs, GLP-1 agonists must be discontinued on the day of surgery and metformin should be discontinued a night before surgery.
- SGLT-2i should be discontinued 3 days prior to surgery.
- In patients undergoing surgery, insulin basal-bolus regimen should be preferred.
- For longer and complex surgeries IV insulin infusion is recommended.
- Monitor blood glucose more frequently ranging from 0.5-2h
- On the day of surgery, avoid alterations in long-acting basal insulin unless there is a tendency of hypoglycemia or if the patient is on diet restriction preoperatively.
- **Basal insulin only**
- • **Once-daily dosing** – Patients with type 2 diabetes who take only once-daily basal insulin (e.g., NPH, glargine, detemir, degludec) may continue basal insulin without any change to their usual regimen, as long as the basal insulin dose has been adjusted appropriately as an outpatient and results in safe morning glucose levels. We often reduce the dose by 10 to 25 percent to lower the risk of perioperative hypoglycemia [1].
- •**Twice-daily dosing** – Patients with type 2 diabetes who take twice-daily basal insulin may also be able to continue their usual regimen. If there is concern about preoperative hypoglycemia, we reduce both doses (morning and prior evening) by 10 to 25 percent.
- ●**Basal and prandial insulin** – For patients (with type 1 or type 2 diabetes) who take two types of insulin (basal **and** prandial), we advise as follows:
- •Omit any prandial insulin (regular, lispro, aspart, glulisine) after fasting begins, typically on the morning of surgery.
- •If basal insulin (eg, NPH, glargine, detemir, degludec) is given once daily in the morning, advise the patient to give between one-half to two-thirds of their usual **total morning insulin dose** (prandial plus basal insulin) **as basal insulin** to prevent ketosis during the procedure.
- ●**Pre-mixed insulin** – Fixed-ratio, pre-mixed insulins are used by some patients with type 2 diabetes for convenience. In this setting, the dose on the evening prior to surgery should be reduced by approximately 20 percent and the dose on the morning of surgery by 50 percent. However often the morning dose ie omitted especially, if the morning blood glucose is <120 mg/dL.[2]
- Patients should be provided with clear instructions about the return to their preoperative OADs and management of hypoglycemia.
- Resume regular OAD medications only after the patient is medically stable and retaining oral meals regularly. Do not resume metformin in a patient with renal dysfunction.
- Non-emergency procedures should be cancelled if patients have metabolic abnormalities (DKA, HHS, etc.) or glucose levels>400 mg/dL
- Multidisciplinary care team within an institution should formulate appropriate protocol to be followed.

Limited Care

- Delay surgery until fluid volume status (BUN, creatinine, and urine output) is stable and metabolic (pH, plasma glucose, creatinine, BUN, electrolytes) control is achieved.
- Tailor the postprandial insulin requirements according to the nutritional mode of patient.
- Avoid consecutive doses of subcutaneous insulin to prevent "stacking" of insulin.

Background

Patients with diabetes experience a higher number of hospitalization and surgeries with longer hospital stays, higher treatment costs and greater risks of morbidity and mortality than non-diabetics. [798-800] Surgeries in patients with diabetes can be categorized as major or minor. Major inpatient surgeries are defined as procedures requiring general, epidural, or spinal anesthesia for ≥1 h and hospitalization for >1 day, while all other outpatient procedures may be defined as minor surgeries. [801,802] Surgical procedures may result in a number of metabolic perturbations that can alter normal glucose homeostasis. Persistent hyperglycemia before and during surgical procedures may lead to postoperative complications like cerebral ischemia, endothelial dysfunction, postoperative sepsis, acute renal failure and surgical site infection (most common complication) and may also impair wound healing in patients with diabetes.[803,804] Surgical stress may lead to hyperglycemic hyperosmolar syndrome (HHS), the most common postoperative complication associated with 42% mortality rate along with diabetic ketoacidosis (DKA) during or after surgery.[802,803,805] Furthermore, increased stress leads to increased counter regulatory hormones causing insulin resistance and the resulting hyperglycemia impairs neutrophil function and triggers overproduction of inflammatory cytokines and reactive oxygen species which causes vascular and immune dysfunction, and cellular damage.[804] Therefore, to minimize these negative consequences and improve the postoperative

outcomes it is important to carefully manage the glycemic level in diabetic patients undergoing major surgeries, including orthopedic and cardiac.[805] The treatment recommendations for patients with T2DM should be individualized-based on the severity of diabetes, their usual standard diabetes regimen, level of glycemic control, and types of surgical procedures (major/minor).[802] Overall, the management goal in diabetic patients undergoing surgery should be optimization of metabolic control, adequate fluid repletion and postoperative care management with or without insulin to improve surgical outcomes. [798,804,805]

Preoperative assessment

Early risk assessments can minimize the incidence of perioperative and post-operative morbidities and reduce mortality rates as it provides an opportunity for planned intervention, proper arrangement, and long-term follow-up.[799] Physicians and multidisciplinary care teams must comprehend a strategic plan to optimize glycaemic management in diabetic patients undergoing surgery.[806]

Perioperative glycemic targets and assessment preoperatively, the ADA recommends a preoperative glucose target of 80 to 180mg/dL as reasonable blood glucose maintenance. It is mandatory that the preoperative evaluation for surgical procedures must be conducted and must include an assessment of glycemic control and the presence of any diabetes-related complications. The critical baseline laboratory data must be assessed to measure serum creatinine level to assess DKD, hemoglobin HbA1c, and blood glucose level.[806] Other critical assessments that must be considered are enumerated below [Table 24].

What is specific managemant of diabetes in surgical patients with diabetes?

The specific management, of surgical diabetic patients will depend on whether the patient is:

- On diet alone/ OHA/Insulin therapy
- Blood glucose level controlled/uncontrolled
- Undergoing Major/Minor surgery
- Undergoing elective/emergency surgery

Major surgery is defined as any operative procedure under general anesthesia for convenience. Management of diabetes will be discussed in various hypothetical groups, which is likely to be encountered in daily practice.

A. Type 2DM/ diet alone/ minor

- No specific change in preoperative therapy is required if patient is able to eat his regular meals.

B. Type 2DM / OHA/ controlled/ minor

- Again no specific preoperative therapy change is required if the patient can eat his regular meals and take drugs. However, monitor blood glucose levels perioperatively and if hyperglycemia (blood glucose >200 mg/dl) occurs insulin infusion can be started as described below.

C. Type 2DM / OHA/ controlled/major/elective

- These patients if on long acting OHA, required to be changed to short acting OHA. Metformin should be discontinued 48 hours prior to and 48 hours subsequently to the procedure to protect against possibility of metformin induced lactic acidosis, risk of which in increased during hypotension and increased anaerobic metabolism. A simple protocol is described below.

Avoid long-acting OHA (Glimeperide)

If on glibenclamide/ glipizide/ gliclazide

1. Omit the morning dose on the day of operation
2. Monitor blood glucose
3. Control hyperglycemia with insulin infusion
4. Restart OHA when oral diet is resumed

D. Type 2DM / OHA/uncontrolled/ major/elective OR

Type 2DM / Insulin treated/major/elective undergoing any surgery These patients will require insulin therapy perioperatively for the control of hyperglycemia and to avoid surgery-related complications.

Preoperative management

Patients treated with oral medications and/or noninsulin injectable Metformin should be discontinued a day before surgery due to the possibility of lactic acidosis with mortality rate of approx. 50%.[807] OADs mainly sulfonylureas and meglitinides, in fasting state have potential to cause hypoglycemia and trigger endogenous secretion of insulin, independent of the glucose level, hence should be discontinued one day before surgery. Further, sulfonylureas and meglitinides increase the risk of myocardial ischemic injury and may be associated with an increased risk of cardiovascular events and mortality.[808] SGLT-2 inhibitors are associated with high risks for DKA and volume depletion. There have been many case reports of euglycemic ketoacidosis in the perioperative setting; hence, SGLT-2 inhibitors should be stopped three days prior to surgery. [809-811]. DPP-4 inhibitors may be discontinued before surgery; however, a recent study establishing the safety and efficacy of sitagliptin alone or sitagliptin in combination with basal insulin in hospitalized medical and surgical patients demonstrated good tolerability and low risk of hypoglycemia and can be considered a viable option in the perioperative setting.[806,812] Due to slow gastric motility, GLP-1 agonists (exenatide, liraglutide) are usually withheld the day before surgery.[809,813] AGIs (acarbose, miglitol) lower glucose absorption after meals, but these agents do not have any effect in the preoperative fasting states, and hence should be discontinued until the patient resumes eating.[816] TZDs should be avoided due to risks like congestive heart failure, fluid retention and peripheral oedema.[812]

Patients treated with insulin

Insulin being the most preferred choice of drug for patients undergoing surgery, the basal-bolus regimen is the best protocol as it is associated with improved glycemic control and lower perioperative complications.[807] Continuing at least part of the basal insulin is the reasonable, physiologic approach to controlling glucose levels before surgery in patients with diabetes. Basal bolus regimens are also associated with reduced postoperative complications and reduced inpatient costs per day. The dose of usual basal insulin can be reduced by 20-30% if the patient reports nocturnal or fasting hypoglycemic history.[817] Long-acting insulins demonstrate fewer peaks and hence do not result in hypoglycemia during fasting. It is advised that long-acting insulins must be taken as close as possible to the usual injection time, preoperatively. The intermediate-acting insulin neutral protamine Hagedorn (NPH) is usually given two times daily. NPH is not a peak less insulin, and there is a chance of hypoglycemia and better be avoided in these settings. Premixed insulins (Combinations of basal and prandial insulin) are not recommended before the surgery.[818] Patients on insulin pumps subjected to longer surgical procedures should be shifted to the IV insulin infusion. Patients on basal-bolus insulin regimen should calculate the total daily insulin dose [Table 25].[803]

Intraoperative management

Endocrine Society and Society for Ambulatory Anesthesia (SAMBA) recommend that intraoperative glucose levels be maintained at less than 180 mg/dL. Glucose levels should be monitored hourly intraoperatively and immediately after surgery. [812,819] For patients with T2DM undergoing major or minor surgery, IV infusion of insulin, glucose, and potassium is recommended to maintain the glycemic targets [Table 26].[802] To maintain the glucose targets intraoperatively, IV insulin infusion regimen-a protocol-driven algorithm is recommended.[806]

Postoperative management

Glucose control in noncritically-ill, non-ICU surgical patients is managed with subcutaneous insulin. During recovery, the glucose levels must be monitored at least every 2-h for all diabetic patients and non-diabetics treated with insulin in the operating room. Correctional subcutaneous rapid-acting insulin doses are provided for BG greater than 180mg/dL Patient should be transitioned to a subcutaneous basal/bolus insulin regimen as soon as the patient can consume solid food. To prevent the insulin coverage gap while transitioning from IV infusion to subcutaneous, after administering the first subcutaneous insulin dose, there should be infusion overlap for at least 1-2-h. Patients previously on an insulin regimen can continue their regular dose provided they are good with eating patterns.

For patients not on insulin treatment previously, depending on the patient's sensitivity to insulin calculate a subcutaneous regimen by totaling 0.2-0.5 U/kg of body weight. The total calculated daily insulin dose is to be divided as 50% basal component (long-acting insulin) + 50% prandial boluses (rapid-acting insulin) and split between breakfast, lunch, and dinner. Patients treated with oral/non-insulin injectables initiate their regular home regimen provided they are regularly eating and are medically stable. Do not resume metformin for at least 2-3 days, especially in patients with renal dysfunction, hepatic impairment or heart failure because of potential risk of metabolic acidosis. [806,812]

Table 31: Preoperative assessments

History	Physical assessment	Baseline assessment
Asses for symptoms of neurologic, cardiac, retinal, renal and PVD Family history of diabetes, nutritional status, eating pattern, weight history, previous or current infection, use of alcohol, tobacco etc. Endocrine disorders, history of acute hypoglycemia, ketoacidosis. Type and duration of diabetes, current treatment regimen along with diet and results of glucose monitoring	Examine BP, feet, skin (insulin-injection site), thyroid. Cardiac examination including resting tachycardia, orthostatic hypotension, stress test or angiography as indicated Airway, neurologic and abdominal examinations	Assessment of serum electrolytes and creatinine level, HbA1c (if not assessed since last 3 months) and BG level Identification of comorbidities and optimize wherever required with the help of a multidisciplinary team
BP: Blood pressure, Glycosylated hemoglobin, PVD: Peripheral vascular disease, BG: Blood glucose		

Table 32: Supplemental insulin dose adjustment

BG (mg/dL)	Usual[a]	Insulin-sensitive[b]	Insulin-resistant[c]
>141-180	4	2	6
181-220	6	4	8
221-260	8	6	10
261-300	10	8	12
301-350	12	10	14
351-400	14	12	16
>400	16	14	18

Numbers in each column represent the number of regular or rapid-acting insulin analogs per dose. Add the "supplemental" dose to the scheduled insulin dose. [a]Given before each meal and at bed-time for the patients able to take all or most of his meals, [b]Start regular insulin every 6 h or rapid acting insulin every 4-6 h for the patients who are elderly, not eating and with impaired renal function, [c]In patients receiving more than 80 U/day before admission and those who were receiving corticosteroids. BG: Blood Glucose

Table 33: Intravenous insulin infusion protocol

Initiate insulin infusion by mixing 100 U short-acting insulin + 100 mL normal saline at the rate of 0.5-1 U/h (0.5-1 mL/h) [a]. Initiate separate infusion of 5% dextrose + water at the rate of 100-125 mL/h. Monitor BG every hour (every 2 h when stable) and according to the following algorithm adjust the insulin infusion rate

BG level (mg/dL)[b]	Action
<70	Recheck BG after turning off infusion for 30 min. If reading still shows <70 mg/dL, give 10 g glucose and keep checking BG every 30 min until the level rises to 100 mg/dL, resume the infusion and reduce rate by 1 U/h
70-120	Reduce insulin infusion rate by 1 U/h
120-180	Continue the regular insulin infusion
181-250	Increase rate of insulin infusion by 2 U/h
251-300	Increase rate of insulin infusion by 3 U/h
301-350	Increase rate of insulin infusion by 4 U/h
351-400	Increase rate of insulin infusion by 5 U/h
>400	Increase rate of insulin infusion by 6 U/h

Prepare an infusion syringe by adding 50 units of insulin to 50 ml of normal saline (1 ml = 1 unit of insulin).

1. Initial rate of insulin infusion and bolus is calculated by measuring the blood glucose and dividing the value by 100 (round off to the nearest whole number or0.5 fraction).
2. Monitor blood glucose hourly and adjust the dose according to the above formula.
3. If blood glucose falls >100 mg/ dl or >20% of the previous level in the first hour, then decrease the calculated insulin dose by 0.5 -1.0 unit.
4. If blood glucose does not fall by 50 mg or 10% of the previous level within 2 hours of starting insulin infusion, then increase the calculated insulin dose by 0.5-1 unit. Maximum limit is 50 units/hour.
5. When blood glucose is <100 mg/ dl, stop insulin drip or pump for 60 minutes. Add 5% dextrose @75-100ml/ hr. Measure blood glucose after 60 minutes. Restart insulin infusion when blood glucose >100

FASTING AND DIABETES

Recommendations

Recommended Care

- Fasting to be avoided in individuals with T2DM especially if they also have:
  - Uncontrolled or unstable glycaemia history of recurrent diabetic ketoacidosis (DKA), significant macrovascular/microvascular complications or hypoglycemic unawareness
  - On intensive insulin therapy or experience frequent hypoglycemic episodes
  - Non adherent to medical nutrition therapy, physical activity and /or pharmacotherapy Antenatal or nursing women or elderly people or children
- People living with diabetes who wish to fast must:
  - Consult a physician prior to fasting
  - Should be encouraged to participate in pre-fast counseling and assessment to optimize monitoring and therapeutic strategies for optimal glycemic control
- During fasting, patients living with diabetes should always:
  - Carry glucose tablets, some sweets or candy to be used in case of hypoglycemia, 15-20 grams of rapid acting carbohydrates can also be useful.
  - Carry an identification card displaying diabetic status and current medication
  - Test blood glucose levels regularly and frequently (especially, if unwell during fasting). Self-monitoring blood glucose (SMBG) as prescribed by HCP can also be performed.
  - Treat promptly if glucose levels are deranged
  - End the fasting immediately in case of dehydration or hypoglycemia and seeks for doctor's help as soon as possible.
  - Discuss with the physician regarding the change in dose, and timing of insulin injections
- Hypoglycemia may be prevented in four levels including primordial, primary, secondary, and tertiary, using the *ASAP (Anticipate, Suspect, Act to treat, Prevent)* strategy
- Metformin, incretin-based therapies (sitagliptin, vildagliptin, and liraglutide) and pioglitazone, glinides, Alpha Glucosidase Inhibitors (AGIs), second generation sulfonylureas like gliclazide MR and glimepiride are the preferable agents to be used during fasting that is spread over a number of days or weeks. In patients on insulin therapy, insulin analogues may be preferred over conventional insulins to minimize the risk of hypoglycemia
- Since prolonged fasting may involve significant reduction in fluid intake so SGLT-2 Inhibitors may be avoided.
- To minimize T2DM-related AEs during fasting, patient centered diabetes education, modified nutrition plan designed for fasting with regular glucose monitoring and adjustment of treatment regimens is recommended.

Background

Fasting is just not merely abstaining from food or 'starving', it is defined as the ability to meet the body's requirements for vital nutrients during either shortage or absence of food, by utilizing the body's energy reserves without jeopardizing health and wellbeing.[1034] Periodic voluntary fasting, is a common religio-cultural practice adopted by individuals from various religions across the world for centuries as a crucial pathway of spiritual purification.[1035,1036] Fasting or food abstinence, initiates metabolic and psychological changes and adaptations that need close monitoring, primarily in patients with derailed metabolism. Therefore, individuals with diabetes or prediabetes must fast only after an appropriate risk assessment and counseling with healthcare practitioners (HCPs) as well as religious leaders and make an informed decision.[1034,1037] In individuals with diabetes, insulin resistance and/or deficiency can lead to excessive glycogen breakdown and a surge in gluconeogenesis or ketogenesis leading to sudden hyperglycemia, diabetic ketoacidosis, dehydration, and thrombosis.[1037] Furthermore, in special populations like pregnant women, geriatric patients and individuals with comorbidities (such as cardiac, renal or hepatic impairment), fasting may increase the risk of complications if appropriate care is not taken.[1038–1040] Therefore, a patient-centric approach with appropriate diet plan and appropriate adjustments in pharmacotherapy with careful glucose monitoring during fasting period may reduce the complications in people living with diabetes. Depending on the degree of abstinence from food, fasts may be classified as follows [Table 32].

Religious fasts

Although religious fasts seldom exceed 24 h, the variability of the duration of every phase may lead to different physiological responses to fasting particularly in people living with diabetes.[1041] Though several guidelines are available for different aspects of diabetes care, fasting in diabetes poses a unique challenge.[1042,1043] Additionally, designing randomized controlled studies to address fasting-related issues in patients living with diabetes is particularly difficult. Therefore, understanding the physiology of fasting [Figure] and linking it to pathophysiology and clinical manifestation of diabetes is required to design strategies for glycemic management during fasting.[1041]

Table 34: Types of fast

Complete fasting: Giving up food and water completely for a period
Partial fasting: Eating less than you need to avoid hunger
Limiting the number of food items eaten
Giving up favorite foods

Figure 18: Structured education program

Table 35: Factors to be modified

Fasting	Antidiabetic agents	Individual phenotype	Patient characteristics
Duration of fast Restriction of fluids/solids: absolute/partial Frequency of fast (once weekly/once monthly/once yearly/others)	Potential for hypoglycemia Potential for dehydration Potential for gastrointestinal upset Duration of action	Risk of hypoglycemia Risk of hypoglycemia unawareness Ability to self-monitor BG	Pregnancy Elderly Concomitant diseases Adolescent and children

BG: Blood glucose

The different religious fasts commonly observed in India that can have a significant impact on metabolic and glycemic health in diabetes is

- Ramadan fasting: It is a principal ritual followed by Muslims during the sacred month of Ramadan (the ninth lunar month of the Islamic/Hijri calendar).[1044] During this month, all healthy adult Muslims abstain from food, drinks, and medication from dawn to dusk (sunset). Believers usually eat two meals, one before dawn (Suhur) and one after sunset (Iftar). Hypoglycemia and dehydration are major complications associated with fasting though hyperglycemia may occur, due to overindulgence in food during meals[12,13] Therefore, pre fast risk stratification, followed by a treatment tailored to individual needs appears to be the best management strategy. In addition, structured education enables patients to self-manage their condition better.[1043–1045]
- Hindu fasts: Though not mandatory, most Hindus observe day-long and week-long fasts. Karva Chauth, Guru Purnima, Ekadashi, Makar Sakranti and Holi Ashtami are some of the annual, monthly and weekly fasts observed as part of various vows. During Navratri, which occurs twice a year, Hindus observe fast for 9 days usually from dawn to moon- rise/star-rise. The day-long paryushan of Hindu fasts however makes it distinct from the

month-long fasts of Ramadan and Buddhist Lent. Unlike Islam, there are no universal rules laid down for Hindu fasts, and therefore data on metabolic effect of these fasts are scanty thus far.[1046,1047]
- Jain fasts: During the pious month of Paryushana (eight days for the Shwetambar sect, and ten days for the Digambar sect), Jains usually fast from dusk to dawn unlike Hindu fasting which extends from dawn to moon- rise.[1036]

Considerations

Based on the following factors the glucose-lowering therapy/ strategy during the fasting period may be modified/altered [Table].

Rationale And Evidence

General

Complete abstinence from food and drink between sunrise and sunset can have a significant impact on homeostasis. Since the majority of diabetic individuals are asymptomatic, they are unaware of the potentially deleterious effects of diabetes, particularly during religious fasts. Additionally, conditions of complete abstinence from food and/or water during religious fast can lead to skipping medications, resulting in worsening of their glycemic control.
- An observational study in Muslim patients with diabetes fasting during Ramadan reports that 59% of patients had substantial knowledge of diabetes, 37% of patients did not monitor their blood glucose levels during the previous Ramadan and 47% had hypoglycemic episodes.[1048]
- In a prospective clinical study conducted in Iran the glycemic control deteriorated significantly among T2DM patients who opted to fast during Ramadan however the HbA1c levels reduced significantly following the month after Ramadan.[1049]
- In an Indian study conducted in 50 patients having type 2 diabetes at a dedicated diabetes care centre, fasting during Ramadan was associated with a reduction in body weight, body mass index & HbA1c level in all patients irrespective of baseline pharmacotherapy but this reduction was statistically significant only in patients taking metformin with DPP inhibitors and/ or SGLT2 inhibitors as compared to patients taking insulin or sulphonylureas at baseline.[1050]
- In a study conducted in Pakistan in 78 patients having diabetes who fasted during Ramadan, body weight increased in 36.7% of participants, decreased in 46.7% with no change in body weight in 16.7% participants . They have also studied the impact of compliance to suggested nutrition plan on body weight changes. In participants complaint to suggested nutrition plan, no weight change was observed in 25% while 66.7% had decreased and 8.3% had increased their weight significantly by a mean of 1.8 kg. However in non-complaint participants, no weight change was observed in 33.3% while only 11.1% had decreased and 56 % had increased their weight significantly by a mean of 2.7 kg. Therefore compliance to suggested nutrition plan is essential for diabetes management during Ramadan.[1051]

DM Education

Concerned physicians and HCPs may play a critical role in educating patients with diabetes during fasting [Figure 19]. Patients and their families should be included in a structured diabetes education program, which provides information about risk stratification, nutritional advice, physical activity, glucose monitoring, identification and management of hypoglycemia, dosage and timing of medications, and identification of the warning symptoms & signs of complications.[1052]

- Implementation of the Ramadan Education and Awareness in Diabetes (READ) program led to significantly lower weight gain ($p<0.001$) and hypoglycemic episodes ($p<0.001$) with reduced risk of acute complications compared to those who were not educated during fasting.[1053]
- As per the survey-based study carried out in India, there was lack of knowledge and awareness about diabetes and impact of fasting on it among patients living with diabetes resulting in a large number of them fasting without medical advice and experiencing events suggestive of hyperglycemia, hypoglycemia and dehydration. Therefore, educational interventions by HCPs prior to Ramadan can help in creating awareness among patients and can help them in making rational decisions about control of diabetes during Ramadan. [1054]
- Self-monitoring of blood glucose (SMBG) and Continuous blood glucose monitoring(CMBG) should be considered as an important tool that helps both patients and physicians to practice safe decision-making regarding drug dosage and other aspects of management.[1055]
- Patients who received individualized education are more likely to modify their diabetes treatment plan during Ramadan, perform self-monitoring of blood glucose at least twice daily during Ramadan, and have improved knowledge about hypoglycemic signs and symptoms as compared to patients who followed the standard diabetes management protocol.[1056]
- Real-time continuous glucose monitoring by offering constant 24-hour recording may improve patients' safety during fasting. Flash glucose monitoring may be a valuable tool in clinical practice during Ramadan avoiding multiple painful finger-pricks in addition to potential of unlimited monitoring times. In children and adolescents with T1DM who used flash glucose monitoring during Ramadan, the risk of life-threatening episodes of severe hypoglycaemia or diabetic ketoacidosis was low. [1057]
- Studies have shown that pre-Ramadan counselling reduces episodes of low blood glucose. Pre-Ramadan education provides a platform to remind people with diabetes about the importance of diet and exercise, and that regular glucose monitoring is essential to avoid complications, while reassuring them that this does not invalidate the fast. The IDF-DAR Practical Guidelines provide healthcare professionals with both background and practical information, as well as management recommendations to optimise the care delivered to people with diabetes who plan to fast during Ramadan.[1058]

Lifestyle modifications and Nutrition during fasting

- Fasting or healthy abstinence from food is a form of lifestyle modification for T2DM patients and if utilized appropriately, may result in several health benefits for these patients.[1059]
- Pre-fasting diet should include slow-release foods and patients with T2DM should not indulge in over-eating in the post-fasting period in order to avoid postprandial hyperglycaemia.[1059] Therefore, complex carbohydrates like whole grains, potatoes, berries, citrus fruits, apples, nuts, and legumes at pre-fasting, and simple carbohydrates like bread, cereals, rice, and pasta at post-fasting may be more appropriate to reduce complications.[1044]
- During prolonged fasting periods like Ramadan or Navaratri, physical activity should be restricted. While routine exercise can be continued, elective moderate to highly vigorous exercise should be rescheduled but total bed rest should be avoided.[1046]

Pharmacotherapy

- Individualized or bespoke treatment choices must be made for oral agents during the fasting period.[1060] Antidiabetic agents that improve insulin sensitivity must be chosen as the risk of hypoglycemia is significantly lower.[1043]

Metformin

Biguanides (Metformin) is generally considered safe in patients with diabetes during fasts due to minimal incidences of hypoglycemia, however, once daily dosing needs to be adjusted or modified to avoid complications.[1061] Slow-release formulations of metformin must be taken once daily following the sunset meal.[1062]

Sulphonylureas and Guinides

Sulphonylureas (new generation: gliclazide MR and glimepiride) should be preferred over older, long-acting sulfonylureas like glibenclamide and chlorpropamide during Ramadan fasting, as they are relatively more safe and economical.[1042,1045,1063,1064] Despite a reduction in dose during Ramadan fasting, Glibenclamide was associated with a high incidence of hypoglycemia due to its longer duration .[1042]Despite a reduction in

dose during Ramadan fasting, Glibenclamide was associated with a high incidence of hypoglycemia due to its longer durationof action and high affinity for its binding receptors. [1065] In two prospective multicentric international randomised trials, gliclazide was demonstrated to have same incidence of hypoglycemia like sitagliptin during Ramadan fasting. Therefore it is safer to use either gliclazide or short acting repaglinide during Ramadan.[1065]

DPP-4

Thiazolidinediones (pioglitazone) are generally regarded as safe during Ramadan, however, it may lead to an increase in body weight. There is only 1 study supporting the use of pioglitazone during Ramadan.[1065,1066] Alpha-glucosidase inhibitors: No RCTs are available about AGI use during fasting currently. However, because of their insulin independent mechanism of action and negligible risk of hypoglycemia, they can be safely used without any dose adjustment during the fasting period.[1067]

- Incretin based treatments may maintain adequate glycemic control in a glucose-dependent manner, thus providing a safe alternative therapeutic option during Ramadan[1043]
- Vildagliptin was found to be effective, safe, and well tolerated in T2DM patients fasting during Ramadan, with a consistently low incidence of hypoglycemia across studies, accompanied by good glycemic and weight control.[1068]
- Switching anti-hyperglycemic treatment to sitagliptin from a sulfonylurea reduced the risk of symptomatic hypoglycemia by approximately 50% in patients who fasted during Ramadan.[1069]
- In Treat 4 Ramadan trial, liraglutide compared with sulfonylurea was well tolerated with more patients achieving target HbA1c, losing or maintaining weight with no severe hypoglycemia, and with a high level of treatment satisfaction.[1070]
- Contrary to the Treat 4 Ramadan trial, no significant difference between liraglutide and sulfonylureas in terms of severe hypoglycemia. However, significant, weight loss and HbA1c reduction ($p<0.0001$) was observed in the liraglutide group suggesting that liraglutide may be considered an effective therapy in combination with metformin during Ramadan.[1071]

SGLT-2i

Sodium-glucose cotransporter 2 inhibitors may be used during fasting, in view of their low risk of hypoglycemia. However, the potential risk of dehydration must be considered. Because of beneficial impact of SGLT2 inhibitors on body weight & hypoglycemia, they can be considered for use during fasting but the potential risk of adverse events related to volume depletion, euglycemic ketoacidosis as well as genitourinary infections and additional risk of falls in elderly due volume depletion in fasting should be kept in mind.

- Treatment with dapagliflozin was associated with fewer incidences of hypoglycemia than sulfonylureas ($p=0.002$).[1072]
- A recent survey report conducted on physicians highlights that SGLT2 inhibitors are safe and effective for T2DM management during Ramadan and (92.2%) of physicians suggested prescribing SGLT2 inhibitors with the first evening meal (Iftar).[1073]
- Till date, there are 3 reported studies about SGLT2 inhibitors use during Ramadan showing beneficial effects on HbA1c, BP and body weight. However, postural hypotension, dry skin and UTI were more common with their use. But ketonemia and deterioration of renal parameters were not observed thereby suggesting safety of these agents during Ramadan.[1065]

Insulin

- Use of a rapid-acting insulin analog instead of regular human insulin before meals in patients with T2DM who fast during Ramadan was associated with less hypoglycemia and fewer PPG excursions.[1074]
- Insulin analogues (basal, prandial and premix) are generally preferred over regular human insulin mainly to minimize the risk of hypoglycemia.[1075]
- In a multinational, randomized, treat-to-target trial in patients with T2DM who fasted during Ramadan, insulin degludec/insulin aspart coformulation (IDegAsp) was having similar glycaemic efficacy as biphasic insulin aspart 30 (BIAsp 30)but with significantly less overall,daytime and nocturnal hypoglycaemia. Therfore IDegAsp is a suitable therapeutic agent for patients who need insulin for sustained glucose control before, during and after Ramadan fasting. [1076]
- As per SOUTH Asian consensus guidelines, Insulin degludec and IDegAsp should be considered drugs of choice for use as basal and dual action insulin before and during Ramadan and IDegAsp can be injected with meals, once daily(depending upon the major meal; either iftar or suhur) or twice daily, or once daily along with an extra dose of insulin aspart. [1077]

Table 36: Approach to adjustment or modification of continued anti-diabetic medications in patients with diabetes during fasting period [1075]

Anti-diabetic agents	Muslim fast		Hindu fast					
	Prolonged	Infrequent but brief	Infrequent but prolonged	Frequent	Jain fast High-risk	Low-risk		Buddhist fast
	Ramadan	Karva chauth	Navratri	Somvaar, Mangalvaar	Tiwihar upavas, Upavas, Bela (Chhath), Tela (Asththam)	Byasana, Ekasana, Ratri Bhojan Tyag		Vaasa
Metformin	• Once daily: take at Iftar • Twice daily: take at iftar & suhur • Thrice daily: take 2/3rd of the total daily dose at the iftar and 1/3rd at the suhur	• Once daily: take at night • Twice daily: take at morning and night • Thrice daily: omit the lunch dose and follow above	• Once daily: take at night • Twice daily: take at morning and night • Thrice daily: take 2/3 of the total daily dose at night and 1/3 at the morning	• Once daily: take at night • Twice daily: take at morning and night • Thrice daily: omit the lunch dose and follow above	Omit the therapy on the day of fast	No change required		No change required
Sulfonylureas*	• Once daily: take at iftar • Twice daily: take ½ of usual evening dose with the suhur and the usual morning dose with the Iftar	• Once daily: take at dinner • Twice daily: omit the morning dose in absence of breakfast	• Once daily: take at dinner • Twice daily: omit the morning dose	• Omit the therapy on the day of fast	Avoided, or taken in half dose at night	Full dose at morning and half dose at night	• Once daily: take at morning Twice daily: take 2/3rd at morning	
DPP-4 inhibitors	• No dose adjustments is required	• No change, take at dinner	• No change, take at dinner	• No change	Omit the therapy on the day of fast	Taken at night	• No change	
SGLT-2 inhibitors†	• No dose adjustment is required and the dose be taken with iftar	• No change, take at dinner	• No change, take at dinner	• No change	Omit the therapy on the day of fast	Evening dose avoided, or taken in half dose	• No change	
Pioglitazone	• No dose adjustments is required	• No change	• No change, or 2/3rd take at dinner	• No change	No change	No change required	• No change	
AGIs	• No dose adjustments is required	• No change	• No change	• No change	Omit the therapy on the day of fast	No change required	• No change	
GLP-1 analogues	• The dose should be titrated 6 weeks prior to Ramadan and no dose adjustment is required	• Reduce the dose to 1/2nd and take at dinner	• The dose should be titrated prior to Navratri	• No change or reduce the dose to 1/2	Once weekly dose: No change (postpone due dosestill the completion of fasting)	No change required		
Long-acting insulin	• Once-daily: ↓ dose by 15-30% and take at iftar • Twice daily: Take usual morning dose at iftar & ↓ evening dose by 50% and take at sahur	• Need no change or may reduce the dose to 2/3rd	• Need no change reduce the dose or may reduce the dose to 2/3rd	to 2/3rd	25% reduction in dose	10-20% reduction in dose		Once daily, before the main meal of 24 hour period
Short-acting insulin	• Take normal dose at iftar and lunch dose at dinner • 1 suhur dose by 50%	Reduce the dose to 1/2th	Reduce the dose to 1/2th	Reduce the dose to 1/2th	1 bolus	2 bolus		Reduce the dose to 1/2th
Premixed insulin	• Once daily: Take normal dose at iftar • Twice daily: Take 1/2 of evening dose with suhur and the usual morning dose with the iftar • Thrice Daily: Omit afternoon dose and adjust iftar and suhur doses	30:70 or 25:75: reduce the dose to 2/3rd 50:50:reduce the dose to 1/2th	30:70 or 25:75: reduce dose to 2/3rd 50:50:reduce the dose to 1/2th	reduce the dose to 2/3rd and prefer 30:70 or 25:75	30:70 at night or 50:50 at day	50:50 once daily		Can be given once daily, before the main meal of the 24 hour period

AGIs, alpha-glucosidase irhibitors; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium-glucose co-transporter-2; *Gliclazide and glimepiride should be preferred among all other sulphonylureas † Elderly patients, patients with renal impairment, hypotensive individuals, those at risk of dehydration or those taking diuretics should not be treated with SGLT2 inhibitors.

Table 37: Dose adjustment/modifications for the management of T2DM during Ramadan fast

Anti-diabetic agents	Current regimen	Recommended dose modification during Ramadan
Metformin	OD	Take at iftar
	BID	Take at iftar and suhur
	TID	Take 2/3 of the total daily dose at the iftar and the other 1/3 at the suhur
Sulfonylureas*	OD	Take at iftar
	BID	Take 1/2 of usual evening dose with the suhur and the usual morning dose with the Iftar
Glinides	The daily dose may be ↓ or divided to 2 doses according to meal size and should be taken at iftar and suhur	
TZD	No dose adjustments is required	
DPP-4 inhibitors	No dose adjustments required	
Acarbose	No dose adjustments is required	
SGLT-2 inhibitors†	No dose adjustment is required and the dose be taken with iftar	
GLP-1 receptor agonists	The dose should be titrated 6 weeks prior to Ramadan and no dose adjustment is required	
AGIs	No dose modification is required	
Long acting insulin	OD	↓ Dose by 15%-30% and take at iftar
	BID	Take usual morning dose at iftar↓Evening dose by 50% and take at suhur
Short acting insulin		Take normal dose at iftar andlunch-time dose at dinner ↓Suhur dose by 50%
Premixed insulin	OD	Take normal dose at iftar
	BID	Take 1/2 of usual evening dose with the suhur and the usual morning dose with the Iftar
	TID	Omit afternoon dose and adjust iftar and suhur doses
		Carry out dose titration every 3 days
Insulin pump	Basal rate	↓ Dose by 20%-40% in the last 3-4 h of fasting ↑ Dose by 0%-30% early after iftar
	Bolus rate	Normal carbohydrate counting and insulin sensitivity principles apply

*Gliclazide and glimepiride should be preferred among all other sulphonylureas, †Elderly patients, patients with renal impairment, hypotensive individuals, those at risk of dehydration or those taking diuretics should not be treated with SGLT2 inhibitors. BID: Twice daily, TID: Thrice daily, OD: Once daily, AGIs: Alpha glucosidase inhibitors, DPP-4: Dipeptidyl peptidase-4, SGLT-2: Sodium-glucose co-transporter-2, TZD: Thiazolidinedione, GLP-1: Glucagon-like peptide 1

Special Population

Pregnant Patients

Many pregnant women with pre-existing diabetes or GDM are considered as high-risk group for fasting. Multiple factors influence the risk assessment of a pregnant women with hyperglycaemia and these should be carefully reviewed prior to fasting. Patient education prior to is essential to ensure mother and foetus safety regardless of fasting decision. Regular SMBG should be conducted and at the very least once before the sunset meal; 1-2 hours after meals; once while fasting; anytime feeling unwell. Pregnant women must understand that regardless of their fasting status, they need to sustain the standard blood glucose targets during pregnancy of:

• Fasting between 70-95 mg/dL (3.9 – 5.3 mmol/L).
• Post-prandial < 120 mg/dL (6.7 mmol/L).

Pregnant women must also understand that during pregnancy they should break their fast if any of the following occur:

• Pregnant women must break their fast if they feel unwell; BG levels drop below 70 mg/dL (3.9 mmol/L); or identify a reduction in foetal movement.
• Patients treated with insulin should have doses adjusted according to their insulin regimen. [1058]

Patients with T1DM

As per the current recommendations, patients with type 1 diabetes mellitus are considered as high-risk to very high-risk for fasting; **and therefore, it is prudent to avoid unsupervised fasting in type1 diabetes.** But with the provision of optimal care (including individualized care, provision of flash glucose monitoring, structured Ramadan and diabetes education sessions and access to a specialist diabetes center), selective patients with type 1 diabetes may fast during Ramadan safely with a low rate of complications including hypoglycemia as per one study carried out in UAE. However larger, randomized controlled trials are required to be able to generalize this as a recommendation.[1078]

As per ISPAD consensus recommendations about fasting during Ramadan for young people with type 1 diabetes, limited high-quality data is available and therefore well-designed, randomized controlled trials are needed to determine optimal insulin regimens to minimize glucose fluctuations. Currently insulin types and regimens should be individualized as per local resources. Most investigators recommend lowering the insulin dose during fasting but recent data do not support this for reduction in the frequency of hypoglycemia. However, they are optimistic about the recent technologic developments such as the newer insulin analogues, "smart" insulin pumps and advanced glucose monitoring devices and telemonitoring which might help young people with type 1 diabetes for safe fasting in the future. [1079]

Elderly Patients

Lower proportions of elderly individuals fast than their younger counterparts. Diabetes related complications such as hypoglycaemia and hyperglycaemia can be more frequent in elderly individuals than in younger individuals during the Ramadan fast. Greater and more careful planning pre-Ramadan is needed in elderly individuals to ensure a safe fast during Ramadan can be achieved.

There must be a greater emphasis on SMBG in elderly individuals during the Ramadan fast to ensure safety.

Antidiabetic drugs with lower risks of hypoglycaemia are preferred in elderly individuals. There is a significant need for more research into elderly individuals with T1DM, T2DM and differing comorbidities that actively fast during these times.[1058]

Recommendations include:

- Increase the frequency of SMBG when fasting before or after meals.
- Consider the using a continuous means of monitoring blood glucose levels if available.
- There needs to be an emphasis on staying properly hydrated, particularly in individuals prone to diabetes related comorbidities.
- It is important to have an adequate intake of nutrients when breaking the fast.
- An individualised nutrition plan should be made prior to fast and adhered to during the entirety of it.

Table 38: Categories of risk in patients with T1DM or T2DM who fast during Ramadan

Category	Parameter	I [very high risk]	II [high risk]	III [low/moderate risk]
Personal characteristics	Life stage	Childhood/adolescence/pregnancy/ lactation/elderly	Late mid age	Healthy adulthood
	Life style	Intense physical labour; potential public health impact of hypoglycaemia, e.g., in commercial drivers	Variable duties, e.g., shiftworkers	Routine life style
	Overall health	Infirm; cognitive dysfunction; severe acute illness	Risk of dehydration; on concomitant steroid therapy	Stable
Diabetes related characteristics	Type of diabetes	Brittle diabetes; T1DM, poorly controlled	T2DM, poorly controlled T1DM, well controlled	T2DM, well controlled
	Acute complications	History of severe hypoglycaemia/ DKA/HHNKC within 3 months prior to Ramadan; history of recurrent hypoglycaemia	None	None
	Chronic complications	History of hypoglycaemia unawareness; CKD stage 4/5; advanced macrovascular	CKD stage 3, stable macrovascular complications	No complication
Therapeutic characteristics	Noninsulin therapy	Conventional sulfonylurea	TID regimes	All other therapy
	Insulin therapy	Basal bolus regimes	TID regimes: Basal-plus; premixed TDS, rapid-rapid-premix; premix-rapid-premix	Once or BID regimes: Basal; premixed analogues
Medico-religious advice	Religious suggestion	Listen to medical advice. Do not fast in health is endangered. Be prepared to break the fast if ill health occurs		
	Medical management	Structured education; SMBG; Dose titration. Watch for complications, and manage appropriately		

T1DM: Type 1 diabetes, T2DM: Type 2 diabetes, DKA: diabetes ketoacidosis, HHNKC: Hyperosmolar hyperglycaemic nonketotic coma, CKD: Chronic kidney disease, TID: Thrice daily

EDUCATION

Recommendations

Recommended Care
• A patient-centered, structured diabetes self-management education (DSME) is recommended as an integral part of the care of all people with T2DM.
• The diabetes self-management education and support (DSMES) program should be conducted at least at four critical times: at diagnosis, annually, when complicating factors arise, and when transitions in care occur, and as considered appropriate.
• Medical professionals can conduct education programs, and certified diabetes educators who are quality assured can provide education (Certified Diabetes Educators) in groups or individual settings. A family member, friend, or caregiver may be involved as needed.
• The education program should focus on people with diabetes from all backgrounds, mainly rural or poorly educated patients, as they may have less knowledge or awareness regarding diabetes. Education material should be customized for those with diabetes from different backgrounds. Every primary care unit should facilitate the training of at least one of their health professionals to become a diabetes educator.
• Diabetes education should be focused on assessing changes in patient behaviors and promoting self-management in patients with T2DM.
• Diabetes education initiatives should be in simple, understandable, and local languages as far as possible.
• The healthcare provider should ensure that DSME programs are accessible to all patients and designed based on considerations of cultural needs, ethnicity, psychosocial status, medical history, family support, literacy, disability issues, and financial situation.
• Use techniques of active learning (engagement in the process of learning and with content related to personal experiences), adapted to personal choices and learning styles.
• Use modern communication technologies to advance methods of diabetes education delivery and channels for intervention such as one-on-one or group sessions and effective use of social media platforms by creating credible source(s) of information for those living with diabetes and their caregivers.
• RSSDI recommends the use of diabetes-related information that is made accessible on the official website of RSSDI and associated social media channels, including but not limited to Facebook, YouTube, Instagram, and Twitter, for improving knowledge and offering an empowering tool to bring positive behavior changes and management skills in those living with diabetes and their caregivers. Although limited, the evidence suggests that using credible sources is associated with improved patient outcomes.
• Provide ongoing diabetes self-management support and the creation of self-help groups. Preventive education for diabetes and metabolic disorders should start at the school level.

Background

Diabetes self-management education (DSME) is a critical component of the management of T2DM, facilitating the knowledge and skills required to improve self-care practices to prevent the development or delay of the progression of diabetes.[1080–1082] Numerous studies report that DSME is associated with improved metabolic control, reduced glycemic levels, fewer complications, and enhanced quality of life (QoL).[1081–1083] DSME initiatives aim to improve the knowledge about diabetes and empower people with diabetes to make informed choices to self-manage their condition more effectively.[1084,1085] It is guided by evidence-based standards while incorporating the needs, goals, and life experiences of patients with diabetes.[1086] The 2022 ADA Standards of Medical Care in Diabetes recommends that people living with diabetes should be actively

engaged in education, self-management, and treatment planning with their health care team, including the collaborative development of an individualized eating plan.[923] The 2022 consensus report by ADA and EASD on the management of hyperglycemia in T2DM recommends that all people with T2DM should be offered access to ongoing DSMES (Diabetes self-management education and support) programs.[1087]

India represents a country with diversity in social, economic, cultural, and educational patterns. The majority of the Indian population resides in rural areas, where there may be differing levels of access to information and education, resulting in decreased awareness of diabetes as compared to urban areas.[1088] No or low literacy in India is a deterrent to a poor understanding of diabetes.[1089,1090] Effective patient education is an essential tool, especially in resource-poor settings within India, especially with the rising prevalence of T2DM across India. Considering the magnitude of diabetes, the increasing prevalence in the younger generation, and the changing patterns of lifestyle impacting future generations, preventive strategies and education should be part of school curricula, workplaces, and offices.

Considerations

The panel endorsed the IDF recommendations on education as such. However, evidence from India and local factors such as literacy, nutrition status, body weight, BMI, and financial background was reviewed in the Indian context and are considered in the recommendations.

Rational And Evidence

Educational programs and their outcomes

- In managing T2DM patients, a structured diabetes care program (Freedom 365*) with education on diet and lifestyle correction, biochemical investigations, clinical monitoring, and treatment at regular intervals was associated with better clinical outcomes compared to routine medical care. The program played a pivotal role in improving the patient's quality of care by overcoming clinical inertia and improving adherence to therapy while preventing the occurrence/progression of diabetes-associated complications.[1091]
- Organized diabetes education that involved improving knowledge for better control of disease symptoms, disease regimens, and risks in practice was found to have a positive impact on lifestyle changes, self-control abilities, and improving the QoL in T2DM patients.[1092]
- A recent systematic review including 118 unique interventions reported that DSME was associated with a statistically significant mean reduction in HbA1c levels (-0.74 for intervention and-0.17 for control groups).[1081]
- A case-control study conducted in the department of medicine of a tertiary care teaching hospital in northwest India demonstrated that effective health education improved knowledge, attitude, and practices leading to better glycemic control that can slow down the progression of diabetes and prevent downstream complications.[1093]
- To minimize the increasing burden of NCDs, the ministry of health and family welfare (MOHFW), Government of India, launched the National Programme on Prevention and Control of Diabetes, Cardiovascular diseases and Stroke (NPDCS) on 8th January 2008, with several objectives including health promotion and health education for the community.[1094] The telephone intervention was found to be statistically significant for empowerment and practices of self-care when compared to group education.
- Besides diabetes, an educational intervention also successfully reduced some of the obesity-related parameters and improved dietary patterns in individuals with pre-diabetes and diabetes. Initiation of primary prevention strategies through education right from elementary schools could reduce IFG by 17%, suggesting such interventions may delay T2DM or even change the course of disease for improved outcomes among vulnerable population groups.[1095]
- Awareness about early detection and treatment of hyperglycemia in pregnancy is also essential, as it is associated with better fetal outcomes and an improved intrauterine metabolic environment. Interventions post-partum should be aimed at the long-term prevention of diabetes, obesity, and metabolic syndrome in the mothers and offspring exposed to intra-uterine hyperglycemia in later life.[1096]
- The world's first national Gestational Diabetes Mellitus (NGDM) Awareness Day was declared by India on the 10th of March, 2019, and is observed every year to raise awareness about hyperglycemia in pregnancy and the link between maternal and fetal health with diabetes. Nationwide, pregnant women are invited to hospitals and clinics for a free screening, especially on that day, and educational activities are also held. There are training programs for healthcare professionals, press conferences, awareness-raising events, seminars for women's groups, and widespread screening activities that are conducted on that day.[1097]
- Defeat Diabetes was a massive public-awareness campaign initiated by RSSDI with the goal to reach a hundred million people in a hundred days using various social media platforms of RSSDI and educating people regarding multiple aspects of diabetes. As part of the campaign, a nationwide blood sugar testing camp was conducted, yielding over 1.1 million blood sugar tests in one day. The success of these endeavors highlighted that coordinated, well-executed campaigns, along with the use of technology, can successfully create public awareness.[1098]

Knowledge and awareness

- The ICMR-INDIAB study reported that the awareness of diabetes in urban India was significantly higher than in rural residents (58.4% vs. 36.8%, $p<0.001$). Furthermore, participants from Tamil Nadu had the highest (31.7) and Jharkhand the lowest (16.3) knowledge score. Among self-reported patients with diabetes, Maharashtra had the highest (70.1), and Tamil Nadu had the lowest score (56.5).[1088]
- Similarly, another ICMR-INDIAB study including 14,277 participants revealed that only 480 patients self-reported diabetes (254 urban and 226 rural), and the level of glycemic control among patients with self-reported diabetes in India was poor.[1099]
- A population-based study from a south Indian state reported that among 6211 participants, good knowledge about diabetes was observed in 3457 (55.6%) individuals and a positive attitude towards diabetes in a total of 3280 (52.8%) individuals, respectively. Furthermore, literacy was significantly associated with good knowledge, attitude, and practice in the T2DM population. Overall, women had significantly better knowledge ($p<0.001$) as compared to men.[1100]
- A recent study from east Delhi, India, reported that self-learning modules (SLM) were associated with significantly increasing knowledge on the effect of diabetes on the feet ($p<0.05$), foot care, and its steps ($p<0.05$) as compared to the control group in T2DM patients.[1101]
- Though general practitioners in India are aware and updated about symptoms and screening for T2DM, there is a dearth of effective approaches towards screening and treating complications. Most patients are usually not advised on non-pharmacological measures or diabetes education, while interpretation of screening test results or its complications may be controversial.[1102]
- Evidence from several studies determining the level of knowledge and awareness on diabetes across India suggests that most patients had poor knowledge and awareness about their condition.[1088,1103–1109] Low socio-economic status, old age, cultural factors, lack of access to healthcare, family history of diabetes, and, importantly, low literacy levels were the significant predictors of poor glycemic control among patients with T2DM.
- A cross-sectional, questionnaire-based survey was conducted on 100 patients attending the diabetes unit of a tertiary care teaching hospital in central India. The majority of these patients were found to be aware of hypoglycemic symptoms, treatment, and the development of complications. The regular check-up was done by 70% of patients, while 73% adhered to treatment.[1110]
- A cross-sectional survey was carried out among participants aged ≥18 years, visiting a tertiary care eye institute in north India to assess people's awareness about various aspects of diabetes. Of the 530 participants interviewed, only 40 (25.6%) individuals with diabetes and 45 (13.8%) without diabetes were aware of diabetic retinopathy. Their knowledge about its risk factors, complications, prevention, and management was poor.[1111]
- In a study conducted on 400 diabetic patients (out-patient or admitted), awareness of diabetic nephropathy was marginally higher in patients staying

in urban areas (vs. rural areas, p=0.120) and among the literate (vs. uneducated, p=0.567) patients. Awareness of diabetic nephropathy was higher in older patients (p=0.004) and patients with chronic diabetes (p<0.0001), controlled diabetes (p=0.026), and diabetic nephropathy (p<0.0001).[1112]

- Study has shown that pharmacists may also be involved with clinicians as a part of collaborative diabetes care and has documented positive clinical, humanistic, and economic outcomes, which emphasized the value of multidisciplinary collaborative care for Asian diabetes patients and supported the effectiveness of this approach in managing chronic diseases.[1113]
- In a review of risks, benefits, and best practices for social media and health care providers, it was concluded that social media platforms offered a rich potential for personal and public health promotion and professional advancement when used with discretion. Guidelines issued by professional societies as well as organizations help health care providers to prevent the downsides of the use of social media.[1114]
- An evidence-based review of social media use in interventions for diabetes clearly outlined that there was limited good-quality evidence on the use of social media interventions for those living with diabetes; nevertheless, these platforms are associated with beneficial patient outcomes, and clinicians and other stakeholders should encourage patients to use the same for knowledge enhancement.[1115] Findings suggested that the primary intervention supported by social media, especially platforms that are the most popular networking sites, improved clinical outcomes for those with T1DM.
- A systematic review of the patients' use of social media for diabetes self-care included studies reporting peer-to-peer use of social media for self-care of diabetes and CVD (with stroke) and found that social media use is evolving and offers great potential. Although there were few studies reported so far on social media and diabetes self-care, they reported interest and demand for peer-to-peer interaction on diabetes self-care. The reviewers felt a distinct need to establish the safety and efficacy of social media use among patients with diabetes and other conditions[1116].
- In the pandemic times, patient education gained center stage as self-management of diabetes was the need of the house. A study evaluating its use as a platform for education and support for people with diabetes used "Tweetorials," "zoom conferences," and "YouTube videos" and found that despite limitations, social media could be effectively used to provide reliable, relevant diabetes education and information, especially allowing people to learn at their own pace. [1117]

Table 39: Recent evidence

Epps A et al., 2019	Whether the use of social media among diabetes specialists across the UK enhances learning on a closed forum, improved communication, sharing of best practices, and provide peer support. Forum where diabetes specialists shared safety alerts, ideas for service improvement, events, scenarios/medication reviews, updates from conferences, and job vacancies.

Challenges in diabetes management in India [1118–1121]

- The awareness of the disease and its complications is less than satisfactory.
- There is a lack of knowledge, appropriate attitude measures, or practice studies that can help determine the gaps in knowledge among physicians and people living with diabetes in India. Physician-related issues, including inadequate knowledge, delay in clinical response, clinical inertia, and poor control, need to be addressed through diabetes education for physicians.
- Lack of knowledge among people living with diabetes is a significant barrier to their ability to self-manage the disease. Hence, having more structured diabetes education programs in India is imperative.
- Lack of a robust referral system to provide quality and specialist care and lack of understanding for early diagnosis, prevention, and control of chronic complications in diabetes. Specialist referral for diabetes management can be a significant challenge in remote and rural facilities with primary care and a dearth of trained diabetes specialists.[1122]
- Indian studies have shown that barriers to insulin therapy partly arise from the lack of awareness, bias, and false beliefs about insulin use and wrong perceptions. People with ongoing insulin therapy appeared to have a better understanding and acceptability of insulin therapy than those who were not on insulin; besides, intensification of insulin therapy remained a challenge in these patients.[1123]
- Implementing efficacious health service interventions like patient education in a real-world resource-constrained setting is not without challenges and may not prove effective in improving patient outcomes. Therefore, interventions must consider patients' and healthcare providers' experiences and perceptions and macro-level policies for translation into practice within local health systems.[1124]
- In India, due to the disease-related stigma, counseling young and probably unmarried women with diabetes on garnering familial support and marital prospects is particularly challenging.[1125]

Assessing the need for evidence-based education [1113,1126–1129]

- Appropriately qualified diabetes educators (nurses, dieticians, social workers, or qualified diabetes educators) should be a central player in raising diabetes awareness as part of optimal diabetes care.
- Continuous medical education and periodic training are needed to help health professionals integrate new knowledge and transform old practices.
- Specialized diabetes education should be made accessible to healthcare personnel and people with diabetes through various communication channels.
- General practitioners and physicians should be periodically updated on recent guidelines related to diabetes, especially on diagnosis, treatment, and management goals.
- Key aim of diabetes education is to promote self-management and help change behavior for better diabetes management.
- Given that diabetes is a complex disease impacted by various factors, empowering language focused on person-first can strengthen communication and help motivate good health and well-being in those with diabetes. According to the expert opinion of the task force from the American Association of Diabetes Educators (AADE) and the American Diabetes Association (ADA), language for diabetes care and education should be neutral, non-judgmental, and based on facts, actions, or physiology/biology; free from stigma; should be strength-based, respectful, inclusive, and imparts hope and is person-centered. [1130]
- Awareness and education in diabetes care in India are required to be improved at the following levels:

- Education and need for continuous medical education of physicians, including family physicians and primary care physicians
- Education for people with diabetes, their family, and caregivers.
- Diabetes education programs in India need to be developed as structured and regionally applicable.

- Counseling is the most crucial strategy to bring about sustainable lifestyle changes.
- Clinic waiting areas may be used effectively to impart diabetes-related education with adequate involvement of family members and caregivers.
- The components of diabetes education are described in this infographic and may not be limited to the same.
- There is also a need to assess the impact of existing education and training programs on diabetes, especially across the Indian diaspora.

Figure 19: Components of diabetic education. CGM: Continuous glucose monitoring; SMBG: Self-monitoring of blood glucose[35]

Implementation

- Major components of implementing the recommendations are the recruitment of personnel and their training on the principles of both diabetes education and behavior change strategies. The staff must develop patient-centered and structured education programs for people with diabetes.
- Educational strategies and materials aligned with the needs of people with diabetes with due consideration of the socio-cultural factors are necessary. Institutional support is critically important at the practice, community, and health care system levels [Figure19].

PSYCHOSOCIAL ISSUES

Recommendations

Recommended Care
Approach to care
• Diabetes management should be carried out within a framework of informed and shared decision-making, following the philosophy of responsible patient-centered care.
• Psychosocial care should be provided to all individuals with T2DM using a collaborative, patient-centered care approach with referral to mental health care professionals where needed.
• Family members and other close ones in the management of diabetes must be involved
• Self-disclosure of diabetes, as opposed to maintenance of confidentiality, should be decided on a case-to-case basis, keeping the sociocultural environment in mind
• HCPs should take care of their own psychosocial health,
• Physicians should consider screening tools for diagnosis of diabetes-related anxiety: Hamilton Rating Scale for Depression and Hospital Anxiety and Depression Scale (HADS), Generalized Anxiety Disorder-7 Scale, Symptom Checklist-90, Diabetes Distress Scale, Diabetes Quality of Life Questionnaire, Hypoglycemia Fear Survey and Diabetes Fear of Injection and Self-Testing Questionnaire
• A careful assessment of depression: use of structured clinical interviews and self-reported measures such as the Beck Depression Inventory, Centers for Epidemiologic Studies Depression Scale, PHQ-9, and HADS. The Geriatric Depression Scale is used to screen for depressive symptoms in older individuals.
• Eating disorders, sexual dysfunction and substance abuse must be screened in patients at risk
• Physicians should asses the socioeconomic status and education profile of the patient while planning therapy.
• Interview of patient's spouse/parent/children (offline or online) for better assessment of patient's psychosocial aspect in Diabetes Mellitus.
• Listening to a patient can be a good way to look into this aspect. But time is the most concerning part. So recorded audio / video of patients can be sent to HCP and within a stipulated time he can revert back to the patient.
Specific interventions:
• The psychosocial needs of specific groups, e. g., children, adolescents, and youth of marriageable age, adults of reproductive age group, antenatal women, the elderly, the marginalized, and members of ethnic/religious minorities must be kept in mind.
• Coping skills training to prevent and manage diabetes distress should be an integral part of diabetes management. Individuals should be taught to integrate positive coping skills and unlearn negative coping.
• Nonpharmacological psychological therapy such as behavioral therapy and cognitive behavioral therapy must be offered when appropriate.
• People with hypoglycemia unawareness should be warned of this problem and the treating physician should relax tight glycemic control in order to restore hypoglycemia awareness.
• Gluco-vigilance must be maintained while prescribing psychotropic drugs that are known to influence carbohydrate metabolism.
• The use of CGM can help to allay the fear of hypoglycemia and help in the improvement of psychosocial well being
• Personalized self-management support programs and the use of social media in patient education, and e-health-based psychological interventions are useful.
• Digital mental health intervention in the form of the peer support element, diabetes-relevant content and examples, and check-in on their mental health and diabetes self-management regularly can ease the overall implementation.
• Group home telemedicine for young adults with T1D will positively affect diabetes distress, self-efficacy, and diabetes-specific communication
• Use of cognitive behavioral therapy help in addressing psychosocial issues.

Limited Care
• Be alert to signs of cognitive, emotional, behavioral and/or social problems which may negatively impact quality of life and complicate self-care, particularly where diabetes outcomes are sub-optimal.
• Refer to mental health specialist advice according to local availability of such professionals.

Background

Complex environmental, social, behavioral, and emotional factors, together known as psychosocial factors, play a crucial role in optimum diabetes management and achieving satisfactory medical outcomes. The daily demands of the disease course and management interrupts the psychological well-being of people with diabetes. The prevalence of comorbid psychosocial problems is greater in patients with diabetes than in the general population.[941] The psychological and social issues such as stress, anxiety, depression, eating disorders, cognitive dysfunction, or other psychological disorders are associated with poor self-care, increased mortality, functional impairment, increased healthcare cost, loss of productivity, and reduced quality of life.[1131–1134] Patient's psychosocial conditions have significant impact on the overall outcomes of diabetic care process.[1135–1137]

Euthymia is a target, as well as a tool, for diabetes management. [1138,1139] Psychosocial well-being comprehends both physical and mental health, and is integral to diabetes- care and self-management. The ADA and the American Association of Diabetes Educators (AADE) have focused on the role of diabetes self-management education and support (DSMES) on improving psychosocial benefits, including the reduction of depression.[1140–1142] In addition, integrating mental health services in diabetes management can help with effective coping strategies. Yoga, or any kind of physical activity tailored for an individual patient can also help in the management and balancing the mental health by improving glycemic control, anxiety, depression, and QOL as well as exercise self-efficacy (ESE).

The IDF 2018 guideline has suggested the inclusion of a mental health professional in the multidisciplinary team and highlighted the need for counselling a patient in the setting of on-going diabetes education and care.[1143]The AAACE has recommended, cultural and faith-based aspects of therapy during counselling.[254]

In India, heterogeneity in linguistic, cultural, religious, socioeconomic, educational, regional, and familial factors affects the clinical progression, treatment and outcome of diabetes management. While family and community support medically-impaired persons as a part of our ethos, societal insensitivity often exhibits itself, as culinary cruelty in many ways for example: Indian patients with T2DM showed a significantly higher perception of burden of social and personal distress associated with the disease, and have been reported to have one of the lowest levels of psychological well-being based on the World Health Organization-5 (WHO-5) Well- being Index.[1141,1144] These challenges and strengths warrant the development of India-specific recommendations for psychosocial management of diabetes, sensitive to and appropriate for, the Indian context.[1145]

Considerations

Diabetes care and self-management is likely to be affected in presence of a mental health disorder that notifies patient's psychosocial condition. Detection of such disorders in relatively brief consultations with diabetes professionals is challenging. There is a need for some basic training to diabetes professionals in management of psychosocial issues, and for appropriate referral approach to mental health professionals with a knowledge of diabetes, especially for seriously affected patients.

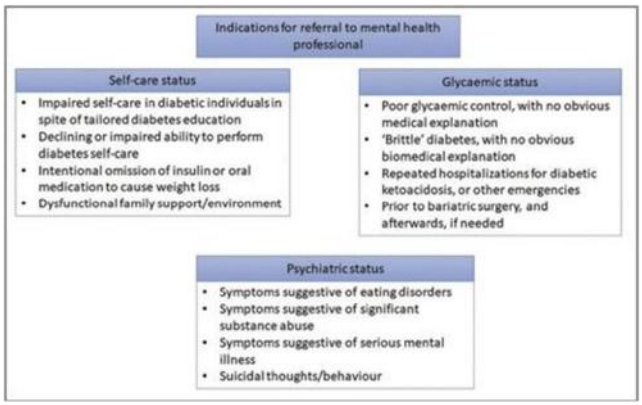


Figure 20: Indications to consider for referral to mental health professional

Rational And Evidence

Challenge

- Diabetes depression and anxiety have bidirectional impact on each other. Being diagnosed with diabetes imposes a life-long psychological burden on the patient and his/her family. Prevalence of clinically significant depression, anxiety, and eating behavior disorder are considerably more common in patients with diabetes than in those without the disease.[1146–1148]
- The findings from a systematic review and meta-analysis conducted on 248 observational studies demonstrated that almost one in four adults with T2DM experienced depression; while depression was more common in patients with <65 years of age compared with elderly. [1149]
- Poor psychological functioning can seriously interfere with daily diabetes self-management, with subsequent poor medical outcomes and high costs. [1150,1151]
- Solution
- Collaborative care interventions and a team approach for diabetes management have demonstrated efficacy in self-management with improved psychosocial outcomes. [1152,1153]
- A systematic review and meta-analysis have shown that, overall, psychological interventions are effective in improving glycemic control in T2DM. [259]
- A randomized-controlled study showed that web-based guided self-help centered on cognitive behavior therapy for people with diabetes with mild-to-moderately severe depression is effective.[1154]
- Psychological counseling can contribute to improved adherence and psychological outcomes in people with diabetes [Figure].[1155]

Implementation

- Major component of implementing these recommendations is the involvement of HCPs and their training on principles of both diabetes education and psychosocial interventions.
- HCPs are required to develop a collaborative, patient-centered medical care strategy for all patients with diabetes to improve health outcomes and quality of life.
- HCPs must be trained in applying psychological assessment tools and monitoring procedures, for diagnosis and periodic evaluation.
- Collaboration with mental health specialists who have knowledge in diabetes can help extend the education and training of other mental health specialists in relation to diabetes.

TYPE 2 DIABETES MELLITUS IN YOUNG AND ADOLESCENTS

Recommendations

Recommended Care
• Risk-based screening for prediabetes and/or T2DM should be considered in asymptomatic children and adolescents, performed after puberty or after ten years of age, whichever occurs earlier. - If tests are normal, repeat testing at a minimum of 3-year intervals or more frequently if BMI increases. • Fasting plasma glucose, 2-h plasma glucose during a 75-g oral glucose tolerance test, and HbA1c can be used to test for prediabetes or diabetes in children and adolescents. - Panel of pancreatic autoantibodies should be tested to exclude the possibility of autoimmune T1DM. - The patient should be evaluated for monogenic forms of diabetes or pancreatic diabetes if clinically indicated [1156]. • Treatment of youth-onset T2DM should include lifestyle management (long-term weight management, vigorous physical activity, healthy eating patterns), diabetes self-management education, self-monitoring of blood glucose, and pharmacologic treatment. • A family-centered approach to nutrition and lifestyle modification is essential, and nutrition recommendations should be culturally appropriate and sensitive to family resources. • Bariatric surgery may be considered in adolescents with marked obesity (BMI: >35 kg/m^2 or 120% of 95th percentile)[1157] and uncontrolled glycemia and/or severe comorbidities despite lifestyle and pharmacologic intervention. • Blood pressure should be measured and optimized to reduce risk and/or slow the progression of diabetic kidney disease. • Youth with T2DM should be screened for the symptoms of other comorbidities, including laboratory studies when indicated for neuropathy, retinopathy, non-alcoholic fatty liver disease, obstructive sleep apnoea, and polycystic ovary syndrome (in female adolescents), cardiovascular disease, and dyslipidemia. • Starting at puberty, preconception counseling should be incorporated into routine diabetes clinic visits for all females of childbearing potential. • Patients should be screened for smoking and alcohol at diagnosis and regularly thereafter.

Background

Until recently, most children and adolescents with diabetes had type 1 diabetes (T1DM). However, the prevalence of T2DM in children and adolescents is dramatically increasing[1158]. The onset of diabetes at a younger age is associated with more prolonged disease exposure and increased risk for chronic complications. Young-onset T2DM essentially affects working-age individuals, further accentuating the adverse social effects of the disease. Asian Indians tend to develop T2DM at a younger age than white Caucasians[1159,1160]; additionally, there has recently been a downward shift in the age (<30 years) at the onset of T2DM in India[1161–1166]. As in adults, the major predisposing diabetes risk factors in children and young adults include obesity, decreased physical activity, family history, and a sedentary lifestyle. In addition, other factors, including prenatal factors (e. g., low birth weight, maternal under-nutrition), the biological propensity to central obesity and insulin resistance, low lean mass, diabetes during pregnancy, impaired glucose tolerance, and urban stress are associated with a high prevalence of T2DM in Indian children and young adults.[1167–1175]

Data on the prevalence of young onset T2DM are scarce worldwide, especially in India[1176]. It has been estimated that 1 in 3 new cases of diabetes mellitus in the USA diagnosed in youth younger than 18 years is T2DM and is more common among youth between 10 and 19 years of age[1158]. A comparison of Indian and Western diabetes registries suggests that young-onset T2DM is less common in Asian Indians than Caucasians. As per the Indian Council of Medical Research- Young Diabetes Registry (ICMR-YDR), 22.8% of youth with diabetes had a diagnosis of T2DM, compared to 70.6% with T1DM[1177]. Data from southern India suggest an incidence rate for T2D of 20.2 per 1000 person-years among adolescents with standard glucose tolerance, followed up for a median of 7.1 years[1178]. A recent analysis of the Comprehensive National Nutrition Survey (CNNS) showed that among adolescents aged 10-19 years screened using HbA1c, the prevalence of dysglycemia (diabetes/prediabetes) was 12.3% and 8.4% among boys and girls, respectively[1179].

Pathophysiology of type 2 diabetes mellitus in young versus adults

The mechanisms of development of T2DM in young people are similar to those in older patients; however, the speed of onset, severity, and interplay of

reduced insulin sensitivity and defective insulin secretion might differ in patients who develop the disease at a younger age[1180]. Studies suggest that loss of β-cell function plays a significant role in the development of T2DM in youth[1181,1182], and that the decline in β-cell function is accelerated in young-onset T2DM compared to older onset T2DM (20–35% per year compared to 7%)[1183]. It has also been suggested that T2DM in adolescents and children might have a more aggressive course compared with adult later onset T2DM[1180]. They also seem to run a higher risk of micro- and macrovascular complications compared to older onset T2DM or even T1DM adjusted for the duration of diabetes [1184–1187].

Screening and diagnosis

The diagnostic criteria for diabetes in children and adolescents are similar to those in adults and include:

Symptoms of diabetes mellitus such as polydipsia, polyuria, and unexplained weight loss plus casual glucose concentration≥200 mg/dL (11.1 mmol/L) in venous plasma, fasting glucose ≥126 mg/dL (7.0 mmol/L) in venous or capillary plasma, or 2-h glucose during OGTT ≥200 mg/dL (11.1 mmol/L) in venous plasma or capillary whole blood or HbA1c ≥6.5%[1188]. Children at substantial risk for the presence or the development of T2DM should be tested. Children and adolescents who are overweight or obese (BMI >90th percentile) and have a family history of T2DM in first-or second-degree relatives must be screened. Children with signs of insulin resistance or conditions associated with insulin resistance such as acanthosis nigricans, hypertension, dyslipidemia, and polycystic ovarian syndrome, must also be screened regularly.[1189]

As the etiology of diabetes in young Asian Indians is heterogenous[1190], the following clinical presentations should alert the clinician to the possibility of other forms of non-type two diabetes in youth.

- Suspect T1DM in youth, family history of diabetes, absence of obesity or signs of insulin resistance, and presentation with severe hyperglycemia with or without ketosis. The presence of pancreatic autoantibodies and lack of endogenous insulin reserve by C-peptide assay (whenever available) will help in making the diagnosis.
- Suspect pancreatic diabetes (fibro calculous pancreatic diabetes-FCPD) in lean youth with features of exocrine pancreatic insufficiency and presentation with severe non-ketosis prone diabetes. Imaging studies (plain X-ray or ultrasound of the abdomen) will reveal evidence of chronic pancreatitis (calculi or duct dilatation).
- Suspect monogenic forms of diabetes (such as maturity-onset diabetes of the young-MODY) in youth with a positive family history of diabetes across three generations, absence of signs of insulin resistance, and non-ketosis prone diabetes. Genetic studies are needed for confirmation of the diagnosis.

Management of type 2 diabetes mellitus in children and adolescents

The ideal treatment goal is normalizing blood glucose values and HbA1c. Weight control is essential for reaching treatment goals and effectively treating T2DM in adolescents. Although lifestyle modification is the most commonly used intervention in adolescents with T2DM, less than 20% achieve or maintain adequate glycaemic control with lifestyle intervention alone[1191]. Aerobic activity, combined with diet, can reduce systolic blood pressure, lower total cholesterol, raise HDL cholesterol, and improve endothelial function in overweight children with T2DM[1192]. Metformin is the most appropriate starting point for pharmacological treatment in children with T2DM. However, results of the TODAY study suggest that monotherapy with metformin was associated with durable glycaemic control in only 50% of children and adolescents[1192,1193]. Insulin therapy is indicated in children with severe osmotic symptoms or marked hyperglycemia with or without ketosis[1194]. Data from the ICMR-YDR indicate a significant proportion of youth with T2DM in India were on insulin. [1177] However, the combination of metformin and insulin has not been shown to improve the durability of glycemic response or promote β-cell [1195] preservation in youth with T2DM. While there has been some recent evidence supporting the use of glucagon-like peptide-1 (GLP-1) receptor agonists (liraglutide, exenatide LAR, and dulaglutide) in youth with T2DM there are no data from India on the use of these agents in this population. [1196] Bariatric surgery has emerged as a viable treatment option in young individuals with T2DM, and evidence has shown that it is safe and effective in obese adolescents. However, clinical data to support this are limited, and the procedure should be considered only after puberty and the attainment of skeletal maturity.

HYPERGLYCEMIA IN PREGNANCY - PRE GDM & GDM

Recommendations

Recommended Care
PRECONCEPTION CARE:
Preconception care and planning should be introduced in all women with diabetes or a history of Gestational Diabetes before planning pregnancy.
Educate about the risks of unplanned pregnancy, its consequences, and the importance of achieving strict preconception glycemic control (HbA1c≤ 6.5%) to minimize these adverse maternofetal outcomes.
Counsel on contraceptives and family planning in all women with diabetes in the reproductive age group.
Insulin is the first line of therapy to treat hyperglycemia in pregnant women with pre-existing diabetes as it does not cross the placenta
General assessment of overall health, including a comprehensive assessment of metabolic status and screening for complications and comorbidities of diabetes: Screen for microvascular complications, including retinopathy and nephropathy, and assess cardiovascular health, especially in women with longstanding diabetes and high cardiovascular risk.
Review all concomitant medications for their appropriateness during pregnancy. Educate about the teratogenic effects of ACEi, ARBs, and statins and the need to stop their preconceptions and switch to safer drug options.
A dose of 400 µg/day of folic acid starting at preconception and continued till 12 weeks of pregnancy should be recommended to avoid neural tube defects.
Comprehensive nutritional and lifestyle assessment, advice, and weight loss assistance should be provided.
Antepartum care:
During the first 10 weeks of pregnancy, offer retinal and renal assessment if not evaluated preconception.
Aim for tight glycemic control with HbA1C 6%, FBS 70-90 mg/dl & 2 hr. PPBS 100-120 mg/dl if these can be achieved without significant hypoglycemia in women with pre-gestational diabetes on intensive insulin therapy.
Insulin is the first-line treatment recommended in all pregnant women with pre-GDM. Basal bolus therapy is most effective in helping achieve these tight glycemic targets.
All human insulins (Regular/NPH) are safe in pregnancy.
Insulin Aspart and Lispro are approved for use in pregnancy although we have insufficient data on glulisine. Insulin detemir has been approved for use in pregnancy, glargine use has been found safe in pregnancy, and Degludec is still not supported for use in pregnancy.
Offer ultrasound monitoring as per protocol to monitor fetal growth and timely detection of any structural abnormalities.
Low-dose aspirin 100–150 mg/day starting at 12 to 16 weeks of gestation may be prescribed to lower the risk of preeclampsia.
Intrapartum care:
Diabetes is not an indication of preterm or cesarean delivery. Pregnancy may be continued to term if maternal metabolic parameters are satisfactory and there are no indications of adverse fetal growth or complications.
Capillary blood glucose should be within the optimum level of 70-110 mg/dL during labor.
Appropriate dose of regular insulin with dextrose infusion must be preferred to achieve target glycemic levels during labor.
Refer to RSSDI recommendations on inpatient hyperglycemia management for detailed insulin management protocol during labor.
Postpartum care:
Monitor blood glucose levels and consider insulin dose reduction to avoid hypoglycemia in women with pre-GDM.
Most women with GDM may return to normoglycemia, and insulin may be stopped post-delivery.
Change glycemic targets to non-pregnant targets as per standard recommendations.
Reassessment of glycemic status at 6-12 weeks postpartum with a 75 gm OGTT in women with GDM. Educate them on the risk of progression to Prediabetes or eventually T2DM and strategies to prevent it.
Recommend breastfeeding
Reminder about the importance of contraception and pre-conception care and planning for pregnancies in the future.

Background

1. Gestational Diabetes and PreGDM

The prevalence of Hyperglycemia in pregnancy is increasing. It includes Gestational Diabetes Mellitus (GDM) and Pregestational Diabetes Mellitus (PreGDM), which consists of all forms of pre-existing diabetes, i.e., Type 2, Type 1 diabetes, and even MODYs.

Conventionally any degree of hyperglycemia detected first time in pregnancy is called GDM. Still, most global organizations term dysglycemia saw the first time in pregnancy in the first trimester (early pregnancy) as pre-existing diabetes in pregnancy. True GDM is diabetes detected for the first time in the second or third trimester of pregnancy which is clearly not overt diabetes.[923]

However, the prevalence of undiagnosed diabetes, as well as prediabetes, is increasing in India. SE Asians have an 11-fold increased risk of developing GDM than Caucasians. Therefore DIPSI recommends universal screening of all pregnant women for GDM at the first point of contact to detect any early GDM to avoid adverse gestational programming of the fetus[1197,1198] as well as to prevent early pregnancy complications.[1197] The DIPSI guidelines endorsed by the IDF, WHO, and FIGO define any manifestation of hyperglycemia in pregnancy as GDM as it represents the detection of chronic β cell dysfunction and is therefore considered a stage in the evolution of Type 2 DM. [1199,1200]

Pre-existing uncontrolled diabetes in women before conception can lead to severe congenital disabilities, spontaneous abortions, and adverse pregnancy outcomes.[1201] The overall prevalence of pre-gestational diabetes has been recorded to be doubled from 1999-2005.[1202] Recent studies have revealed that the prevalence of pre-existing diabetes in pregnant women is 3.4%-3.8%, most of whom were suffering from T2DM.[1203,1204] Gestational diabetes can have deleterious effects on pregnancy, leading to maternal, fetal, and perinatal complications. The complications include still-birth, spontaneous abortion, pre-eclampsia, perinatal mortality, low birth weight, respiratory distress, neonatal death, neonatal hypoglycemia, etc. [1205–1207]

2. Screening criteria (Where, when, and How)

DIPSI recommends a non-fasting Oral Glucose Tolerance Test (OGTT) with 75g of glucose with a cut-off of ≥ 140 mg/dl after 2 hours, whereas WHO (1999) recommends a fasting OGTT after 75g glucose with cut-off plasma glucose of ≥ 140 mg/dl after 2-hour. [1208,1209 1210,1211]

3. Screening and management for diabetes complications

Early screening of diabetes complications like retinopathy, neuropathy, heart failure, and chronic kidney disease in the pre-conception period is essential as they can be life-threatening and associated with lower quality of life for both the mother and the fetus if not diagnosed or treated at an early stage. Poorly controlled pre-gestational diabetes may lead to end-organ severe damage that may result in life-threatening conditions. These complications can be controlled or prevented with appropriate diabetes management.[1212] Diabetic retinopathy is the leading cause of blindness, and there can be a worsening of retinopathy during pregnancy. Women with diabetes who become pregnant should have a comprehensive eye examination before pregnancy or as soon as pregnancy is confirmed in the first trimester. They should be monitored closely throughout pregnancy, at the first visit, if not assessed within the previous six months, then once in each trimester. Diabetic nephropathy is estimated to be present in 5–10% of diabetic pregnancies, and progression to end-stage renal disease has been reported in several women. Also, women with pre-existing diabetic nephropathy are at significantly higher risk for obstetric complications, such as hypertension, uteroplacental insufficiency, and iatrogenic preterm birth because of worsening renal function.[1213] Hypertension, especially in the presence of nephropathy, increases the risk of preeclampsia, uteroplacental insufficiency, and stillbirth.[1214]

Self-monitoring of fasting and postprandial blood glucose should be done, while pregestational diabetes pre-prandial monitoring can be considered. Lower SMBG limits are based on normal pregnancy values. HbA1c may be helpful as a secondary measure of glucose control in pregnancy but secondary to SMBG. HbA1c targets are lower in pregnancy due to increased red cell turnover, ideally below 6%, relaxed to -7% if there is frequent hypoglycemia, and requires more frequent monthly monitoring.

Pre-gestational diabetes is a risk factor for acute myocardial infarction during pregnancy. Pregnancy may be contraindicated in patients with pre-existing coronary artery disease due to the hemodynamic changes that may occur during pregnancy, causing myocardial infarction and death.[1215] Recalcitrant nausea and vomiting due to gastroparesis result from diabetic neuropathy in pregnant women. Gastroparesis impacts the interaction between diet and diabetes regimens and complicates glycaemic control, thereby increasing the risk of hypoglycaemic episodes.[1216] Diabetic ketoacidosis is a life-threatening emergency observed in 5–10% of all pregnancies complicated by pre-gestational diabetes. Common clinical presentations include abdominal pain, nausea and vomiting, and altered sensorium. Hypoglycemia and Hypokalemia are frequent complications of diabetic ketoacidosis management. Hence, glucose and potassium concentrations should be monitored closely.[1217,1218]

Table 40: Checklist for preconception care for women with diabetes [1211]

Preconception education should include:
• Comprehensive nutrition assessment and recommendations for:
- Overweight/obesity or underweight
- Meal planning
- Correction of dietary nutritional deficiencies
- Caffeine intake
- Safe food preparation technique
• Lifestyle recommendations for:
- Regular moderate exercise
- Avoidance of hyperthermia (hot tubs)
- Adequate sleep
• Comprehensive diabetes self-management education.
• Counseling on diabetes in pregnancy as per current standards, including the natural history of insulin resistance in pregnancy and postpartum; preconception glycemic targets; avoidance of DKA/severe hyperglycemia; avoidance of severe hypoglycemia; progression of retinopathy; PCOS (if applicable); fertility in patients with diabetes; genetics of diabetes; risks to pregnancy including miscarriage, stillbirth, congenital malformations, macrosomia, preterm labor and delivery, hypertensive disorders in pregnancy, etc.
• Supplementation
- Folic acid supplement (400 µg routine)
- Appropriate use of over-the-counter medications and supplements
Medical assessment and plan should include:
• General evaluation of overall health.
• Evaluation of diabetes and its comorbidities and complications, including DKA/severe hyperglycemia; severe hypoglycemia/hypoglycemia unawareness; barriers to care; comorbidities such as hyperlipidemia, hypertension, NAFLD, PCOS, and thyroid dysfunction; complications such as macrovascular disease, nephropathy, neuropathy (including autonomic bowel and bladder dysfunction), and retinopathy.
• Evaluation of obstetric/gynecologic history, including the history of cesarean section, congenital malformations or fetal loss, current methods of contraception, hypertensive disorders of pregnancy, postpartum hemorrhage, preterm delivery, previous macrosomia, Rh incompatibility, and thrombotic events (DVT/PE).
• Review of current medications and appropriateness during pregnancy.

Screening should include:
• Diabetes complications and comorbidities, including comprehensive foot exam; comprehensive ophthalmologic exam; ECG in women starting at age 35 years who have cardiac signs/symptoms or risk factors and, if abnormal, further evaluation; lipid panel; serum creatinine; TSH; and urine protein-to-creatinine ratio.
• Anemia
• Genetic carrier status (based on history):
- Cystic fibrosis
- Sickle cell anemia
- Tay-Sachs disease
- Thalassemia
- Others, if indicated
• Infectious disease
- Neisseria gonorrhea/Chlamydia trachomatis
- Hepatitis C
- HIV
- HPV
- Syphilis
Immunizations should include:
• Rubella
• Varicella
• Hepatitis B
• Influenza
• Others, if indicated
Preconception plan should include:
• Nutrition and medication plan to achieve glycemic targets before conception, including appropriate implementation of monitoring, continuous glucose monitoring, and pump technology.
• Contraceptive plan to prevent pregnancy until glycemic targets are achieved.
• Management plan for general health, gynecologic concerns, comorbid conditions, or complications, including hypertension, nephropathy, retinopathy; Rh incompatibility; and thyroid dysfunction.

DKA - Diabetic Ketoacidosis; DVT/PE - Deep Vein Thrombosis/Pulmonary Embolism; ECG, Electrocardiogram; NAFLD - Non-Alcoholic Fatty Liver Disease; PCOS - Polycystic Ovarian Syndrome; TSH – Thyroid Stimulating Hormone.

4. Optimization of antidiabetic regimes

No OADs are approved for pre-existing diabetes in pregnancy, although glyburide and metformin have been used in multiple RCTs for GDM. Minimal data on thiazolidinediones or metiglinides and no data on incretin-based DPP-4 inhibitors and GLP-1 analogues are available.[1219] However, none of these are found safe and are hence not recommended in pregnancy. Metformin and glyburide have been used during pregnancy, but these drugs cross the placental barrier and should be replaced with insulin therapy at the earliest.[1212,1219,1220] Recent data on glyburide has raised safety concerns, including an increased risk of neonatal hypoglycemia. Potential problems for SGLT2 inhibitors in pregnancy due to profound polyuria in a pregnant patient with familial renal glycosuria have been reported. Since pregnancy causes polyuria and glycosuria generally due to increased glomerular filtration rate, SGLT2- inhibitors are not expected to be beneficial and are not recommended.[1219] Metformin has also been associated with prematurity, and long-term follow-up in metformin is still awaited. MITY Study showed SGA in infants exposed to metformin intrauterine. Further studies have shown increased visceral adiposity, increased head circumference, and subscapular skin fold thickness, and further increased adiposity and weight gain in children exposed to metformin during pregnancy.

Insulin does not cross the placenta and is the first choice to attain the target glycaemic goal in pregnant women with pre-existing diabetes.[1220,1221] Basal bolus regimen is ideal in diabetes with pregnancy. Considering alterations in the physiology of pregnant women, daily SMBG is required more frequently, and insulin doses must be optimized at different stages of pregnancy as per requirement.[1221] Insulin requirements may increase as the pregnancy progresses, and the requirement peaks between 28 and 32 weeks of gestation.[1216] Insulin pump therapy is also considered beneficial in maintaining target glycemic control in pregnant women with pre-gestational diabetes without any increase in the risk of hypoglycemia. However, the cost of therapy and the risk for marked hyperglycemia or DKA due to insulin delivery failure from inadvertent mechanical error could be an issue.[1219]

Women with pre-existing diabetes are at a high risk of preeclampsia. Hence the American College of Obstetricians and Gynecologists recommends the use of low-dose aspirin (81 mg/day) prophylaxis to be initiated between 12 weeks and 28 weeks of gestation (ideally before 16 weeks of gestation) and continued until delivery.[1216]

5. Optimization of anti-hypertensive medications [Table 31]

Use of ACE inhibitors and angiotensin receptor blockers (ARBs) as antihypertensive agents are contraindicated in women with pre-existing diabetes and planning pregnancy as these medications are teratogenic and can cause intra-uterine growth retardation, fetal renal dysplasia, and oligohydramnios.[1212,1220–1222] A large randomized controlled trial in pregnant women with pre-existing or gestational hypertension showed that targeting a diastolic blood pressure (BP) of 85 mmHg vs. 100 mmHg reduced neonatal respiratory complications and rates of severe maternal hypertension (i.e., >160/110 mmHg).[1223] Labetalol, methyldopa, diltiazem, nifedipine, clonidine, and prazosin are safe anti-hypertensives during pregnancy. Use of atenolol is not recommended in pregnancy. Chronic diuretics are also not recommended as they are associated with restriction of maternal plasma volume that leads to a reduction in uteroplacental perfusion.[1220] Severe preeclampsia and acute hypertension management may be treated with vasodilators like hydralazine during pregnancy.

6. Management of dyslipidemia

Dyslipidaemia identified during pregnancy should be treated with diet and exercise intervention and glycemic control if indicated. A lipid profile at preconception in women with Familial Hypercholesterolemia (FH) must be conducted and a target level of LDL cholesterol, HDL cholesterol, and triglycerides as <100 mg/dL (2.6 mmol/L), >35 mg/dL (0.905 mmol/L) and <105 mg/dL (1.7 mmol/L), respectively must be established.[1224] The use of statins is contraindicated during pregnancy due to teratogenicity.

Preconception planning and care [Table 41]

Before conception, a set of treatment regimens that aim to optimize social, metabolic, and psychological aspects in a woman with pre-gestational diabetes (T1DM and T2DM) or a history of GDM in previous pregnancy is referred to as pre-conception management.[1220] minimize pregnancy complications and congenital malformations, it is essential to introduce preconception care in the primary care plan for all women with childbearing potential.[1225]

Early diagnosis, optimized glycemic control, proper nutrition, lifestyle modification, and regular follow-up can help in successful pregnancy in people with diabetes. The introduction of multidisciplinary clinics in managing pregnancy with diabetes can reduce the rate of adverse maternal outcomes and perinatal mortality and improve neonatal care.[1226]

Counseling

The pre-conception counseling process should be discrete, concise, and considerate and must provide a clear explanation with sensitivity to social and cultural conventions. Women with pre-existing diabetes should be counseled about the need for contraception till target glycemic control is achieved before going ahead with the planned pregnancy.

Table 41: Elements of a preconception plan

Counseling	Assessment of medication	Glycemic control	Supportive investigation and management
Need for contraception and effective measures The risk associated with unplanned pregnancy Financial/family planning Need for strict glycaemic control and insulin	Potentially teratogenic drugs Use of oral hypoglycaemic agents Insulin therapy Use of insulin analogs	Risk of hypoglycemia Risk of maternal and fetal complications due to hyperglycemia Educate on self-monitoring of BG	Optimum HbA1c level Urine albumin: Creatinine ratio Lipids Test for HIV, HBV, HCV, VDRL, pap smear, rubella, TSH, and fundus Cardiac evaluation
HbA1c: Glycosylated Hemoglobin, BG: Blood Glucose, HIV: Human Immunodeficiency Virus, HBV: Hepatitis B Virus, HCV: Hepatitis C Virus, TSH: Thyroid Stimulating Hormone			

Patients must be counseled and prescribed appropriate contraceptive measures until the metabolic parameters are relevant to conceive. Since the primary goal for glycemic management in the preconception period and during the first trimester is to obtain the lowest HbA1c levels possible without hypoglycemia, women should be made aware that they can have a planned conception only with HbA1c, preferably less than 6.5% to lower the risk of congenital anomalies.[1220,1226] Critical complications with T2DM, such as hypertension, intrauterine growth retardation, and risk of obesity, along with their preventions and management, should be explained to the patients during pre-conception counseling.[1220] Pregnant women with pre-existing diabetes must be advised to avoid fasting. However, religious fasting is a personal decision, and a practical approach should be explained with emphasis on the risks to the mother and the fetus.[1227] Pre-conception counseling must minimize the risk of pregnancy complications in girls and women in their reproductive age with diabetes. Such counseling can improve the mother's health and reduce cost burdens for the mother and the child.[1221]

Glycemic target-preconception and antepartum

It is recommended that women with T2DM who are planning pregnancy should be switched from oral or noninsulin injectable hypoglycemic agents to insulin before conception, if possible. The primary goal of women with pre-gestational diabetes is to maintain optimal glycemic levels. Effective measures must be taken to maintain the ideal glycemic value while minimizing the risk of hypoglycemia. The IDF recommends a pre-conception HbA1c level of <7%, whereas ADA and National Institute for Health and Clinical Excellence (NICE) recommend an HbA1c level lower than <6.5%, provided it is safely achieved.[1212] To prevent chances of spontaneous abortions and major congenital malformations, target HbA1c must be as close to normal as possible without significant hypoglycemia.[1215] HbA1c should be assessed monthly due to the changing kinetics of RBCs and physiological alterations in glycemic aspects in pregnancy.[1220,1221] The ADA recommends HbA1c testing during fasting, SMBG monitoring, and pre-prandial and postprandial in pregnant women with diabetes.[1221] In women with pre-existing diabetes, provision of basal and prandial insulin needs with intensified insulin regimens (multiple-dose regimens of subcutaneous long-and short-acting insulins) are known to give the best results. Rapid-acting insulin analogues, as a part of a basal-bolus regime or via an insulin pump, give better postprandial control. Pre-prandial monitoring can help in dose adjustment of insulin regime and insulin pump. Monitoring of postprandial blood glucose aids in lowering the risk of preeclampsia and macrosomia.

Table 42: Glycemic target in women with pre-existing Type 2 diabetes mellitus before and during pregnancy

Condition	Glycemic target
Fasting	70-95 mg/dL (3.9-5.3 mmol/L)
1-h postprandial	110-140 mg/dL (6.1-7.8 mmol/L)
2-h postprandial	100-120 mg/dL (5.6-6.7 mmol/L)

Table 43: Safety of medicines for diabetes before and during pregnancy

		Noninsulin glucose-lowering agents
	Compound	**Effects on pregnancy**
Class		
SU	Glimepiride	Intrauterine death, skeletal deformities, and fetal growth retardation.
	Glipizide	Crosses placental barrier
	Glibenclamide	It may cross the placental barrier and increases neonatal hypoglycemia. Long-term safety data in offspring of mothers exposed to glibenclamide is not available.
Biguanide	Metformin	Crosses placental barrier and shows congenital malformation; however, lower in rate than those not on metformin medication; increased risk of prematurity.
α-glucosidase inhibitors	Acarbose	
Meglitinides	Nateglinide Repaglinide	Transfusion through the placental barrier is unknown yet. May produce a risk of developmental toxicity in the fetus at a lower risk.
TZDs	Pioglitazone	Crosses placenta, delayed fetal development, reduced fetal weight, and post-implantation losses.
	Rosiglitazone	Crosses placenta, causes fetal growth retardation, fetal death, and placental toxicity.
Insulins		
Rapid-acting analog	Aspart, Lispro, and Gluisine,	Insulin Aspart is known to be most effective in managing glycemic control without causing the risk of hypoglycemia during preconception and throughout pregnancy. Lispro was found to be safe and effective in maintaining BG levels. No safety and efficacy data are available on the use of glargine and glulisine in pregnancy. Determire is safe in pregnancy with an ample amount of data supporting it.[1228] Degludec insulin in pregnancy has no data currently for its use in pregnancy. Though there is no RCT available for the use of Glargine in pregnancy, based on safety data, it is recommended that if the patient is already on glargine insulin and if the treating clinician feels that withdrawing glargine may deteriorate the glycemic control, then on clinician's discretion, glargine may be continued in pregnancy. Detemir is safe in pregnancy and is recommended for its use. The safety of degludec has been shown in a recent publication in Type1DM. Still, it is yet to be recommended for use in pregnancy by any global organization or drug authority.[1228]
TZDs: Thiazolidinediones, BG: Blood glucose		

Antepartum care

Folic acid supplementation

Periconceptional folic acid supplementation decreases the occurrence and recurrence of neural tube defects (NTDs). Hence, in preconception counseling, patients should

Table 44: Safety of medicines for complications of diabetes before and during pregnancy

Class	Compound	Effects on pregnancy
ACEIs	Lisinopril, Perindropril, Enalapril, Moexipril, Trandolapril and Quinapril	Usage of ACEI and ARBs to treat hypertension should be avoided during pregnancy as they severely affect the control over renal function and also fetal and neonatal BP. They may also cause oligohydramnios and skull defects.
ARBs	Losartan, Telmisartan	
Statins	Atorvastatin, Rosuvastatin, Fluvastatin	Usage of statins in the reduction of elevated levels of cholesterol should be avoided in pregnancy as well as in lactation as they may cause congenital malformation.
Lipase inhibitor	Orlistat	Obesity treatment in pregnancy with orlistat shows a low risk to the fetus and should be used cautiously during pregnancy.
ACEIs: Angiotensin Converting Enzymes, ARBs: Angiotensin Receptor Blockers, BP: Blood Pressure		

be educated on the folic acid requirement.[1229] Women with pre-existing diabetes who are planning to become pregnant must be advised to take folic acid (5 mg/day) until 12 weeks of gestation to reduce the risk of having a baby with a neural tube defect.[1212]

Nutrition therapy and weight gain targets

The primary aim of nutritional therapy in pregnancy is to provide calories for normal growth and development of the fetus while maintaining optimized glycemic control and normalizing dyslipidemia. Due to physiologic changes that follow pregnancy, caloric requirements are increased during the second and third trimesters.[1230] Wholesome food choices with 40–50% calories from complex, high-fiber carbohydrates, 15–30% calories from protein, and 20–35% calories from primarily unsaturated fats) are commonly advised.[1216] To fulfill the additional dietary needs, diets are often altered or modified for the amount and type of carbohydrates consumed during pregnancy. It is advisable to include a diet rich in omega-3 fatty acids and non-starch polysaccharides with a low glycemic index and avoid excess intake of saturated fats and TFAs that can lead to an increased risk of complications. Legumes, unprocessed fruits, and vegetables should be included in the diet. Vitamin D supplementation (10 μg/day) is prescribed for women at risk of vitamin D deficiency during pregnancy. Folic acid supplementation with a recommended dose of 400 μg/day is prescribed until 12 weeks of pregnancy to prevent the risk of neural tube defects. Vitamin A supplementation, liver and liver products rich in vitamin A should be avoided as they may be teratogenic. Iron supplements are not often prescribed during pregnancy as they might be associated with unpleasant maternal side effects. ADA suggests the Dietary Reference Intakes (DRI) be
• >175 g of carbohydrate, >71 g of protein, and about 28 g of fiber in all pregnant women.[1212,1215,1221,1231]

Weight management

Obesity is a significant complication in women with pre-existing T2DM; hence, weight management is essential to avoid CV risk in pregnancy. ADA recommends that the weight gain of overweight women during pregnancy should be 15–25 lb whereas, for obese women, it should be 10–20 lb.[1221] Maintenance of weight gain targets during pregnancy can be easily done with the help of an appropriate dietary plan along with lifestyle interventions. Yoga, either individually or combined physical activity, has been remarkably helpful in weight management. Orlistat, a lipase inhibitor shows a low risk to fetal development; hence obesity/overweight in pregnancy can be treated with caution and close monitoring.

Intrapartum care

Glycemic targets during labor and delivery

The timing and mode of birth must be discussed during antenatal appointments, especially during the third trimester. If there are metabolic or other maternal or fetal complications, elective birth before 37 weeks for women with type 1 or 2 diabetes must be considered.[1212] Studies have suggested that the blood glucose target should be maintained at 100-126 mg/dL to prevent hypoglycemia in neonates. It was found that neonatal hyperglycemia is at higher risk when the maternal blood glucose level reaches >180 mg/dL. In a retrospective analysis including 137 singleton cases, mothers with a blood glucose level of about 72-144 mg/dL (4-8 mmol/L) resulted in 87% (n=26) neonatal hypoglycemia, of which 13 neonates were admitted to ICU. These 13 neonates were born with maternal blood glucose levels >144 mg/dL (8 mmol/L). Thus, blood glucose must be monitored closely and controlled within the targets.[1232] The capillary plasma glucose must be monitored every hour during labor and birth in women with diabetes and ensured that it is maintained between 70-110 mg/dL (3.9-6.1 mmol/L) in women with pre-existing T2DM.[1212] Monitoring should be carried out 2-h to 4-h during the latent stage; the active stage requires monitoring every 1-2 h and every hour in patients on glucose infusion. During labor, women with pre-gestational diabetes generally should undergo continuous intrapartum electronic fetal monitoring.[1216] To achieve target glycemic levels, IV dextrose and insulin infusion during labor and birth may be considered for women with diabetes whose capillary plasma glucose is not maintained between 70-110 mg/dL. Rapid-acting insulin analog like aspart or lispro are the preferred choice in achieving the target glycemic value as they minimize the risk of hypoglycemia.[1221]

Postpartum management

Care of newborn

Neonates born to women with pre-existing T2DM are at a higher risk of morbidities like macrosomia, hypoglycemia, respiratory distress, cardiomyopathy, hematologic disorders, and hypocalcemia.[1233] It is recommended to admit babies showing signs of the above morbidities to the NCU postpartum for proper care and management.[1216] To minimize neonatal complications, adequate control of diabetes in the antenatal period and newborn surveillance by a neonatologist are required.[1220]

Glycemic control

Insulin requirement falls in the postpartum period by 34% more than in the preconception period. Over the next 1-2 weeks postpartum, insulin requirement returns to that required during the pre-conception period. Women on insulin should be closely monitored to avoid the risk of hypoglycemia during breastfeeding. Monitor maintenance of pre-feed capillary plasma glucose level of the neonate and assure it to be 40mg%

Lactation

Breastfeeding should be encouraged in women with pre-existing diabetes. There is a sharp decline in the insulin requirement after delivery; hence, the insulin dose needs to be adjusted accordingly.[1220] Dietary care to prevent the risk of obesity is of prime concern during lactation. Strict blood glucose control for women with pre-existing diabetes who underwent cesarean section is essential to avoid infection. Advise a snack before starting to breastfeed, especially to women on insulin, because lactation is energy-intensive and can cause hypoglycemia in the mother if she feeds on an empty stomach. During lactation, women with pre-existing diabetes can resume or continue to take metformin and insulin. ACE inhibitors, ARBs, oral hypoglycemics, obesity medicines, and statins should be avoided during breastfeeding.[1212]

Postpartum contraception

One of the significant barriers to effective preconception care is unplanned pregnancy. To minimize the risk of congenital malformation due to pre-existing diabetes and its complications, it is important to remind women in the postpartum period about the use of effective contraception and family planning. For women who do not choose permanent contraception with tubal ligation, long-acting reversible contraception with an intrauterine device or implantable progestin are the most effective forms of contraception and should be recommended.[1234]

DIABETES AND HYPERTENSION

RECOMMENDED CARE

- Measuring BP in diabetes patients
  - Major goals for the treatment of diabetes are to prevent or delay complications and optimize the quality of life. The pathogenic relationship between T2D and hypertension is assumed to be bidirectional.
  - Elevated BP levels are supposed to reflect at least partially the impact of the underlying insulin resistance on the vasculature and kidneys, while there is clinical evidence suggesting that disturbances in carbohydrate metabolism are more common in individuals with hypertension.
  - Ideal management of chronic conditions, such as T2D and hypertension, often includes monitoring lifestyle changes and pharmacological interventions to improve metabolic health.
  - Home BP measurement has been recommended by many hypertension guidelines and addresses several limitations of traditional office-based care, including reducing misclassification because of white-coat or masked hypertension and an ability to take more suitable action and a course of corrective therapy.[1235]
- Types of Hypertension:
  - Systolic Hypertension
  - Non-Dipping Hypertension
  - Nocturnal,
  - B.P Variability
- The recommended BP targets 1230 for individuals with diabetes should be <130/80 mm Hg and <140/80 in elderly patients. BP should be performed at every clinical visit.1231
- Use of risk calculator1231 to estimate the 10-year risk of a first ASCVD event (available online at tools.acc.org/ASCVD-Risk-Estimator-Plus) is recommended for assessment of better stratify ASCVD risk and help guide therapy.
- First-line therapy for hypertensive individuals and individuals with urine albumin-to-creatinine ratio $300 mg/g creatinine (A) or 30–299 mg/g creatinine (B). If one class is not tolerated, the other should be substituted. B should include a drug class
  - ACEI and ARB 1232
  - CCB and/or thiazide-like diuretic
  - The treatment should include a statin in primary prevention if LDL-C >70 mg/dL (1.8 mmol/L) (diabetes with target organ damage) or >100 mg/dL (2.6 mmol/L) (uncomplicated diabetes)
- Serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored.
- Multiple drug therapy is often indicated in case of chronic kidney disease,
- The therapeutic strategy should include lifestyle changes, body weight control, and the effective treatment of the other risk factors to reduce the residual cardiovascular risk.
- For individuals with hypertension and Chronic kidney disease, RAS inhibitors are first-line drugs as they reduce albuminuria in addition to BP control. CCBs and diuretics (loop-diuretics if eGFR <30 ml/min/1.73m2) (160/100) can be added.
- eGFR, microalbuminuria, and blood electrolytes should be monitored.1233
- Patients with **resistant hypertension** who are not meeting blood pressure targets on conventional drug therapy with three agents, including a diuretic, should be referred to a certified hypertension specialist.
- Individuals on antihypertensive treatment, and home blood pressure should be measured to promote patient engagement in treatment and adherence.
- In pregnant patients with diabetes and pre-existing hypertension treated with antihypertensive therapy, systolic or diastolic blood pressure targets of 120-160/80-105 mmHg is suggested to optimize long-term maternal health and fetal growth.
- All hypertensive patients with diabetes should monitor home blood pressure to identify white-coat hypertension.
- **Orthostatic measurement** of blood pressure should be performed during the initial evaluation of hypertension and periodically at follow-up, or when symptoms of orthostatic hypotension are present, and regularly if orthostatic hypotension has been diagnosed.

Dietary recommendations:

- The American Heart Association recommends no more than 1500 mg of sodium/day as ideal.
- For seasoning of foods, herbs, spices, lemon, lime, vinegar, or salt-free seasoning blends make a better choice than table salt.
- In rice and other cereal preparations like roti, and poori, do not mix salt. Avoid the use of salted rice, salted porridge, and other salted cereal mixes.
- Avoid packaged mixes, canned soups, or broths - they generally have a high sodium content.
- Use fresh vegetables. Avoid the use of canned vegetables as they contain salt preservatives.
- Substitute fruits, salad, and fresh vegetables for salted snack foods.
- Limit the use of foods packed in brine, such as pickles, pickled vegetables, and olives.
- Use little or no sauces: avoid tomato ketchup, soy sauce, MSG, mustard sauce, and chutney.
- Use fresh poultry, fish, and lean meat rather than the canned, smoked, or processed types.

Background

Hypertension and Type 2 diabetes are commonly existing comorbidities.1234 The prevalence of diabetes and hypertension in India is high across all geographical settings and socioeconomic groups in middle and old age. The crude prevalence of diabetes and hypertension was 7.5% (95%CI, 7.3%-7.7%) and 25.3% (95%CI, 25.0%-25.6), respectively.1235 New-onset Diabetes Mellitus is 2.5 times in hypertension, 20 to 40% of IGT patients have HTN, 40 to 50% of Type 2 DM have hypertension, and only 1/4 of HTN in DM is controlled. Cardiovascular risk in patients with both diabetes and hypertension is 3-fold.

Individuals with high blood pressure often show insulin resistance and have a higher risk of developing diabetes than normotensive individuals. It has been observed that over the last 30 years, the prevalence of insulin resistance has increased significantly. Accordingly, hypertension and insulin resistance are strongly related to an increased risk of impaired glucose tolerance, diabetes, cardiovascular diseases, and endocrine disorders.1236 In addition, the major cause of morbidity and mortality in diabetes is cardiovascular disease, which is exacerbated by hypertension. Both conditions are closely interlinked because of similar risk factors, such as endothelial dysfunction, vascular inflammation, arterial remodeling, atherosclerosis, dyslipidemia, and obesity. There is also substantial overlap in the cardiovascular complications of diabetes and hypertension-related, primarily to microvascular and macrovascular disease. Common mechanisms, such as upregulation of the renin-angiotensin-aldosterone system, oxidative stress, inflammation, and immune system activation, likely contribute to the close relationship between diabetes and hypertension.

Various RCTs have been conducted in this field. ACCORD BP, ADVANCE BP, Hypertension Optimal Treatment (HOT), and SPRINT examined the potential benefits of intensive versus standard blood pressure control. However, the relevance of their results to people with diabetes is less clear. ADVANCE BP showed that the intervention reduced the risk of the primary composite end point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%). A 6-year observational follow-up found a reduction in risk of death in the intervention group attenuated but still significant.

SPRINT trial1237 showed that the intensive systolic blood pressure target lowered the risk of the primary composite outcome by 25% (MI, acute coronary syndrome, stroke, heart failure, and death due to CVD), and the intensive target reduced the risk of death by 27%. Intensive therapy increased the risks of electrolyte abnormalities and acute kidney injury.

Diabetic patients are believed to have salt-sensitive hypertension, with high glomerular blood pressure and a flatter pressure-diuresis curve. Hyperinsulinemia caused by insulin resistance is also involved in accelerating the reabsorption of sodium from the renal tubules. Excessive salt intake inhibits nocturnal blood pressure reduction. Morning hypertension has a significantly higher frequency of developing nephropathy and retinopathy.

Rationale and Evidence 1238

- The Hypertension Optimal Treatment (HOT) trial 1231 was a large trial of almost 19,000 patients randomized to a target diastolic BP of 90 mm Hg, 85 mm Hg, or 80 mm Hg. Felodipine was used as baseline therapy, with the addition of ACE inhibitors or β-blockers and diuretics as needed. A subgroup of 1501 with diabetes attained diastolic BPs of 85 mm Hg, 83 mm Hg, and 81 mm Hg, respectively, with a 51% reduction in CV endpoints in the lower compared with the high BP group.
- The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial,1231 evaluated antihypertensive therapy with the ACE inhibitor perindopril and the diuretic indapamide vs. placebo in patients with Type 2 diabetes having a baseline BP 145/81 mm Hg. Mean BPs attained were 134/74 mm Hg vs. 140/76 mm Hg, leading to a lower combined rate of major macrovascular and microvascular events (15.5% vs. 16.8%), as well as a reduction in CV mortality (3.8% vs. 4.6%) and all-cause mortality (7.3% vs. 8.5%).

- The BP arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial 1231 prospectively investigated whether lower BP at such levels further reduced CV events in high-risk patients with Type 2 diabetes, followed during an 8-year period. In the hypertension arm of the trial, 4733 patients aged 40 to 79 with type 2 diabetes were randomly assigned to intensive therapy, targeting a systolic BP of<120 mm Hg, or standard therapy, targeting a BP of<140 mm Hg. The patients had diabetes for an average of 10 years. During the follow-up period of 4.7 years, the average systolic BP was 119 mm Hg in the intensively treated group and 133.5 mm Hg in the standard therapy group. No significant differences were found between the intensive group and the standard group in rates of a combined end point of nonfatal myocardial infarction, nonfatal stroke, or death from CV causes (208 CV events in the intensive group, 237 events in the standard group)
- The ADVANCE study was a 22-factorial intervention with both BP and glycemia treatment, providing another opportunity to look at the combined effect of both interventions. During the duration of 4.3 years, BP was reduced by an average standard error of the mean of 10.3 mm Hg systolic and 90.2 mm Hg diastolic in patients assigned to joint treatment compared with those assigned to neither treatment (P<.001). Similarly, hemoglobin A1c was reduced by 0.61% to 0.02% after 4.3 years of follow-up in patients assigned to joint therapy compared with those assigned to neither treatment (P<.001). Comparing the four resultant groups, glucose-intensive and glucose-standard with and without perindopril indapamide, patients assigned to both intensive glucose and BP-lowering, compared with the standard glucose and placebo BP intervention, had significant 18% and 24% reductions in total and CV mortality and a 28% reduction in renal events, in particular with 54% reduction in the likelihood of new-onset macroalbuminuria.
- The large screening camping1239 conducted in India in 2017 and 2018, was named May Measurement Month (MMM). In 2017, it was found that, out of the 122685 screeners for whom all three BP readings were available, 38974 (31.8%) had hypertension based on the mean of the second and third reading or the history of anti-hypertensive medication. A total of 17205 (14.0%, n=122 685) participants were on anti-hypertensive treatment. Among 17205 participants receiving hypertension treatment, 14203 (82.6%) had uncontrolled BP. In 2018, it was identified that out of all the participants, 64.0% (n=221039) had measured their BP for the first time in their life, and only 28.1% (n= 97 015) recorded their BP within the last 12 months. 81% (n= 279 643) were not on antihypertensive medication. This screening campaign shows that the burden of hypertension in India is high, and such initiatives help identify the hidden cases of hypertension.
- The other study conducted in India on middle-class urban subjects found a low prevalence of normotension and high prevalence of hypertension1240. Normotensive individuals had a lower prevalence of cardiometabolic risk factors than members of the prehypertensive or hypertensive groups. Half of the hypertensive group were aware of having hypertension, a third were receiving treatment for it, and a quarter had a controlled BP

Implementations

Clinical Management for Hypertension in Diabetics

- Blood pressure should be monitored at each visit.
- Use the non-dominant arm unless the dominant arm has 10 mmHg or greater BP compared to the non-dominant.
- Adjust the settings to correspond to bedtime and time awake.
- Ask them to stop and stand still when a reading is being taken (if possible).
- Test an initial reading to be sure it's working.
- Use a proper-sized cuff.
- A thin sleeve over the arm and under the monitor helps prevent bruising.

ADA guidelines: blood pressure targets

- The American Diabetes Association (ADA) defines hypertension as SBP ≥ 140 mmHg and DBP ≥ 90 mmHg confirmed during separate clinic visits. Current ADA guidelines recommend a treatment goal of SBP < 140 mmHg and DBP < 90 mmHg for most patients with diabetes.
- For individuals with diabetes and hypertension at higher cardiovascular risk (existing atherosclerotic cardiovascular disease [ASCVD] or 10-year ASCVD risk > 15%), a blood pressure target of < 130/80 mmHg may be appropriate if it can be safely attained.
- For individuals with diabetes and hypertension at lower risk for cardiovascular disease (10-year atherosclerotic cardiovascular disease risk < 15%), treat to a blood pressure target of < 140/90 mmHg.
- In pregnant patients with diabetes and pre-existing hypertension, a blood pressure target of ≤ 135/85 mmHg is suggested to reduce the risk for accelerated maternal hypertension and minimize impaired fetal growth.
- For patients with blood pressure > 120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderating alcohol intake, and increased physical activity.
- Patients with confirmed office BP ≥ 140/90 mmHg should adopt lifestyle therapy and have prompt initiation and timely titration of pharmacologic therapy to achieve BP goals.
- Patients with confirmed office BP ≥ 160/100 mmHg should adopt lifestyle therapy and have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce CV events in patients with diabetes.
- An ACE inhibitor or ARB, at the maximum tolerated dose indicated for BP treatment, is the recommended first-line treatment for hypertension in patients with diabetes and UACR ≥ 300 mg/g creatinine (A) or 30–299 mg/g creatinine (B). If one class is not tolerated, the class should be substituted.
- For patients treated with an ACE inhibitor, ARB, or diuretic, serum creatinine/eGFR and serum potassium levels should be monitored annually.
- Selection of anti glycemic drugs also plays a vital role in hypertension control and CV Risk reduction.

Risk Factors

Diabetes is associated with both macrovascular (involving large arteries such as conduit vessels) and microvascular (involving small arteries and capillaries) disease. 1241 Chronic hyperglycemia and insulin resistance play an essential role in the initiation of vascular complications of diabetes and involve several mechanisms, including increased formation of advanced glycation end products (AGEs) and activation of the receptor for advanced glycation end products (RAGE) AGE-RAGE axis, oxidative stress, and inflammation. Hypertension is a significant risk factor for diabetes-associated vascular complications because hypertension itself is characterized by vascular dysfunction and injury.

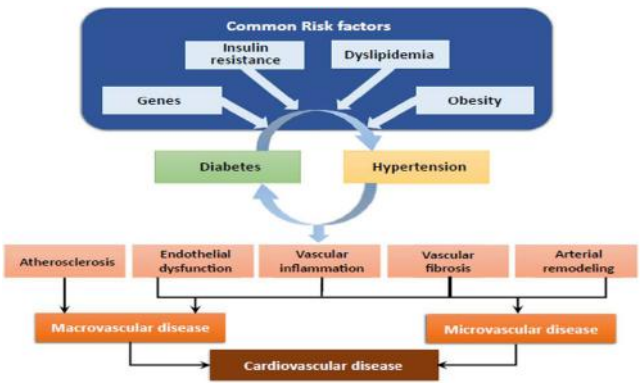


Figure 21: Common Risk Factors

Pathophysiology

The pathophysiology of hypertension in diabetes involves maladaptive changes in the autonomic nervous system, vascular endothelial dysfunction, enhanced activation of the renin-angiotensin-aldosterone system, immune function alterations, and harmful environmental factors. 1242

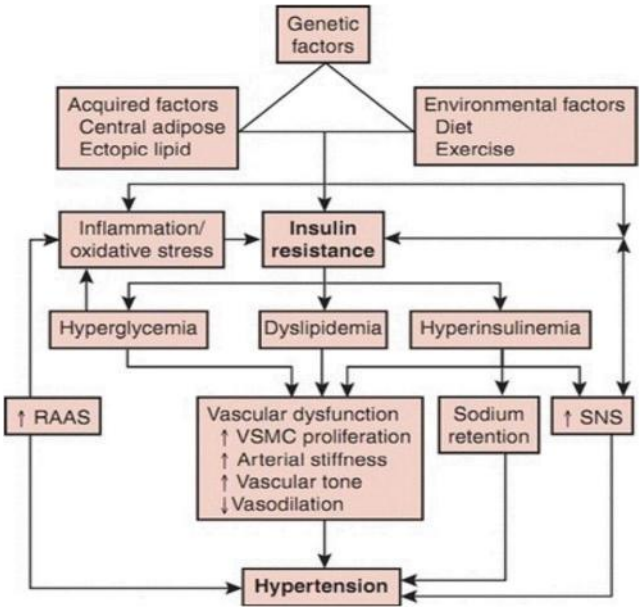


Figure 22: Pathophysiology

Complications

Patients with diabetes have more isolated systolic hypertension, have enhanced variability in BP, are prone to develop orthostatic hypotension, and have HTN, which is more resistant to treatment. Experience less reduction in nocturnal BP and higher baseline heart rates than their non-diabetic counterparts because of autonomic neuropathy; BP control in these patients presents a significant challenge because the target BP is relatively low, and the response to treatment is often poor. Together these conditions fall under the umbrella of metabolic syndrome. And individuals with metabolic syndrome are at increased risk for cardiovascular disease.

Arrhythmia during hypoglycemia is likely the reason for increased CVD deaths observed during strict blood glucose control. The relative risk of CVD occurring during severe hypoglycemia is reported to be 2.05-fold

Microvascular complications:

Action in Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation (ADVANCE) trial cohort has confirmed that microvascular complications increase the risk of cardiovascular complications in individuals with Type 2 diabetes. Moreover, the coexistence of hypertension and retinopathy is a risk factor for the progression of nephropathy. 1241

Orthostatic hypotension (decrease in systolic blood pressure of 20 mmHg or a reduction in diastolic blood pressure of 10 mmHg within 3 mins of standing when compared with blood pressure from the sitting or supine position) is common in people with Type 2 diabetes and hypertension. It is associated with an increased risk of mortality and heart failure.

Considerations

In diabetic patients with hypertension, it has been argued that intensive BP control is more beneficial than tight glucose control. For stroke, any diabetic endpoint, death from diabetes, and microvascular complications, treating hypertension led to much more significant relative risk reductions than treating hyperglycemia. 1243

Treatment Considerations

Treatment Goals

For individuals with diabetes and hypertension at higher CV risk (existing ASCVD or 10-year ASCVD risk < 15%), a blood pressure target of <130/80 mmHg may be appropriate if it can be safely attained. For individuals with diabetes and hypertension at lower risk for CVD (10-year ASCVD risk < 15 %), treat to a blood pressure target of < 140/90 mmHg.

ACEI and ARB are the first lines in the management of diabetic hypertensives. ACEIs may be used alone for BP lowering but are much more effective when combined with a thiazide-type diuretic or other antihypertensive drugs. They reduce the macrovascular and microvascular risks associated with diabetic hypertensives.

Calcium Channel Blockers (CCB) with Thiazide-like diuretics are the second line of treatment.

The renin-angiotensin-aldosterone system is a major regulatory system of CV and renal function. Thus, multiple clinical trials in past decades have confirmed that suppression of renin-angiotensin-aldosterone system activity might be expected to reduce CV mortality and all-cause mortality. Despite the above findings, however, the cardioprotective effects of renin-angiotensin-aldosterone system blockade were recently called into question. The Non–Insulin-Dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril (DIABHYCAR) study found that angiotensin-converting enzyme inhibitors (ACEIs) did not affect CV events in patients with type 2 DM and albuminuria.[1250] There was a higher rate of fatal CV events with Olmesartan therapy among patients with type 2 DM in the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study. [1251]

The American Diabetes Association recommends that patients with DM and hypertension should be treated with a pharmacologic therapy regimen that includes an ACEI or an angiotensin II receptor blocker (ARB). If one class of medication is not tolerated, the other class should be used. Both types of drugs limit the effects of angiotensin II, but the mechanisms of action are not identical. Thus, theoretically, there might be relevant differences between the drug classes. The recent meta-analysis by Van Vark et al. showed that ACEIs or ARBs had different effects on all-cause mortality in patients with hypertension. This difference might also exist in the treatment of DM. However, evaluating the relative effects of ACEIs and ARBs is difficult due to inadequate head-to-head trials. In light of the above, we undertook the present meta-analysis aiming to overcome this limitation by evaluating the effect of ACEIs and ARBs separately vs. placebo or other medications on the incidence of all-cause mortality, CV deaths, and CV events in patients with DM.[1252]

Prevention of Hypertension with diabetes

1 Optimal glycaemic control: While optimal glycemic control remains paramount in the prevention1242 of microvascular complications (retinopathy, nephropathy, and neuropathy), concurrent cardiometabolic derangements such as hypertension and dyslipidemia play a pivotal role in the initiation and progression of macrovascular disease (ischemic heart disease, stroke, and peripheral vascular disease). Effective management of diabetes should therefore include a multifaceted approach combining optimal control of blood pressure and lipids with appropriate glycemic control.

2. Dietary Approaches to Stop Hypertension trial (DASH)1244

Lifestyle modifications such as exercise and a diet low in sodium, saturated fat, and cholesterol and high in potassium, calcium, fiber, and fruits have decreased BP. The DASH diet recommends keeping salt intake to less than 2300 mg (1500 mg daily – elderly). The DASH study compared three eating plans: A plan that includes foods people regularly eat without intervention; a plan that provides for regular food plus more fruits and vegetables alone; and the DASH eating plan, i.e., diet more in potassium, fruits, fiber, calcium and less in sodium, saturated fat, and cholesterol. All three plans included about 3 000 mg of sodium daily. Participants who followed the plan that included more fruits and vegetables and the DASH

eating plan had reduced BP, but the DASH eating plan had better control.

DIABETES IN ELDERLY
Recommendations

General

- India's population of older adults, including those with diabetes, is increasing by enormous proportions.
- Strong emphasis on cost-effectiveness and simplification of management strategies is needed for the care of diabetes in older adults.
- Motivational counseling, cognition enhancement, and social support should be essential tools to improve treatment compliance by older adult diabetic patients.
- Because of significant heterogeneity among older adult diabetic patients, treatment should be tailored according to individual needs to achieve desired glycemic goals.
- Improving subjective well-being and quality of life is an essential care component, particularly for older adult diabetic patients.

Geriatric Syndromes-detection and management

- Many geriatric syndromes like dementia and frailty compromise the abilities of older diabetics to self-manage their disease and they begin depending on a caregiver.
- Older diabetics should undergo screening for early detection of neurocognitive impairment and dementia annually or earlier if there is a deterioration in clinical status. Increasing difficulty in self-management of diabetes should be regarded as a clinical deterioration.
- Older diabetics should undergo screening for early detection of frailty, preferably even before the pre-frail stage, so that its progress can be arrested or reversed, to improve diabetic care in older adults.

Lifestyle Management

- Eating right is described in the chapter on medical nutrition therapy (MNT). Indian diet is high in carbohydrates and low in protein which promotes weight gain and central obesity on one hand and muscle loss (sarcopenia) and frailty on the other. Frailty detection and its management are dealt with in the chapter on geriatric syndromes.
- Physical activity and exercise lower blood glucose, promote cardiac function, improve muscle mass, prevent frailty, strengthen bone mass, and elevate mood. Independent and fit older diabetics can engage in 150 minutes of brisk walking per week, roughly 30 minutes of walking each day for five days a week. On average, they should also be advised to perform muscle strengthening exercises three times a week. However, all exercises should be tailored under medical advice, and the extent and type of physical activity recommended should consider cardiorespiratory reserve and the status of joints, bones, vision, nerves, muscles, etc. Usually, if one can count his pulse rate or record by finger pulse meter, he can check that joint exercises like brisk walking should not raise the heart rate beyond 95 to 120 per minute for those aged 50-60 years, 85 to 110 per minute for those aged 60-70 years and 80 to 105 per minute for those aged more than 70 years[1254].
- Stress management and promoting good sleep in older diabetics can be achieved by de-stressing mechanisms like meditation, music, social networking, befriending grandchildren, etc. Sleep hygiene includes going to bed at least 1-2 hours after dinner, avoiding daytime naps, keeping the room free from noise and bright light, avoiding TV, coffee, tea, and alcohol, and drinking excess water before sleep. Sound sleep is good for preventing or controlling many diseases like diabetes, high blood pressure, heart disease, stroke, depression, dementia, etc.
- Older diabetics should be subjected to periodic health check-ups as a thorough medical examination, including necessary laboratory tests. Checking and monitoring all medications, assessment of teeth, nutrition, urinary problem, depression, and physical and mental disabilities like impaired vision, mobility, hearing, and memory should be a part of health check-up[1255]. The need for any vaccination, especially the pneumococcal and flu vaccination, is also important[1256].
- Miscellaneous steps include avoiding excess alcohol, self-medication, exposure to pollution, smoke, dust, and weather extremes. House should be well ventilated, and inside the house, there should not be any poor lighting, slippery and wet floors, loose fitting carpets, cluttering of furniture, any stairs without railings, or toilets without support grips because all of these make the elderly vulnerable to falls, injuries, and fractures.

Medical Nutrition Therapy

In elderly diabetics with obesity, medical nutrition therapy plays a significant role.
Foods with a low glycaemic index, complex carbohydrates, and high fiber are advised.
Food supplements rich in protein and fiber and fortified with vitamins and minerals may be used.

- Food habits and foods available in the area should be discussed with the patient & relatives.
- Body weight and sugar levels, and comorbidities should be taken into consideration.
- Carbohydrate content should be limited to 50%-60 % of total calorie intake. Complex carbohydrates and high fiber diet should be advised.
- High glycaemic index foods should be discussed and their disadvantages should be explained.
- Fiber intake should be about 25-30 gm per day, but it should not result in diarrhea
- Protein intake should be maintained at about 15% of total calorie intake. The quantity of protein intake depends on age, sarcopenia, and renal dysfunction.
- Fat intake should be limited (<30% of total calorie intake). Avoid consumption of foods with high amounts of saturated fats (butter, coconut oil, margarine, ghee). Saturated fatty acids (SFAs) intake should be less than 10% of total calories/day (<7% for individuals having high triglycerides).
- A diet rich in fruits, leafy vegetables, nuts, fiber, whole grains, and unsaturated fat should be recommended.
- The diet should include pulses, legumes, unprocessed vegetables, and low-fat dairy products.
- Overall salt consumption should be <5 g/day.
- Meal plans with strategic meal replacements (partial or complete) may be an option under supervision when feasible.

Oral Antidiabetic Agents

Elderly diabetics are to be treated with tailor-made therapy. This will depend upon their disabilities, comorbidities, support system and financial status. Elderly diabetics with physical disabilities are given leverages for their physical condition. Nutrition and exercise play an essential role. A careful watch should be kept for drug interactions and ADRs. Recommendations for the use of OADs in elderly diabetic patients are listed below.

- **Metformin**- First line of drug, especially in obese diabetics.
- **Sulfonylureas**- First/Second line of drug.
- **Meglitinides**- May be given.
- **Alpha-Glucosidase Inhibitors**- May be given.
- **Pioglitazone**- May be used in low doses.
- **DPP4 inhibitors**- Good drug, weight neutral, renal & cardiac friendly except vildagliptin in CLD.
- **Oral GLP- 1 Receptor Agonist**- in obese Diabetics
- **SGLT2 inhibitors**- Recommended for up to 70 years of average weight/obese elderly, helpful in patients with diastolic dysfunction.

Injectables

- Injectable therapies like insulin and GLP1RA offer reasonable glycaemic control in elderly diabetics if used with caution, and the appropriate patient selection is made judiciously.
- Starting low and going slow should be the mantra to avoid adverse effects.
- Patient and caregiver education, monitoring, and regular follow-ups are the key to the success of injectable therapies in elderly diabetics.
- Ultra long-acting insulins like degludeg and glargine U300 are the insulins of choice in elderly diabetics.
- Newer ultra short-acting prandial insulins are preferable to cover prandial peaks.
- In case of frequent hypoglycaemic events, especially nocturnal hypos, the nighttime prandial insulin should be stopped.
- The type of insulin and the insulin regimen(e.g., basal only, basal plus, basal-bolus, or premix) should be chosen based on individual patient characteristics.
- SMBG (self-monitoring of blood glucose) and Individualised insulin titration charts are the keys to sustained euglycemia.
- GLP1RA, like dulaglutide, lixisenatide, and liraglutide, offers the same pleiotropic benefits even in elderly diabetics. Starting with the lowest dose possible and slow up-titration will allow for better tolerability of these agents in elderly diabetics.

Hypoglycemia in Elderly

- Hypoglycemia and its unawareness is more common among older diabetics than young diabetics and is fraught with dreadful consequences.
- Hypoglycemia in the elderly is defined as any blood sugar level below 70 mg/dl, and a glucose value of 70–100 mg/ dL should raise the alarm of the need to change or adjust the regimen. Although HbA1c alone should not be the sole criteria for glycemic control, HBA1c < 7.0 should also be taken as a warning for overtreatment
- Liberal relaxation of glycemic targets is essential to avoid hypoglycemia among older diabetics who are functionally dependent or/and are under long-term or end-of-life care. Even functionally independent older patients are vulnerable to hypoglycemia if tight blood glucose control is attempted. Oral hypoglycemic agents can also be withdrawn amongst them if there is a high risk of hypoglycemia.
- An individualized care plan is required, including the desired blood glucose range to minimize the risk of hypoglycemia. This includes both pharmacological and non-pharmacological treatment.
- Among OHAs, sulfonylureas are not the preferred class of drugs as they can cause hypoglycemia. Still, if at all, shorter-acting sulfonylureas like gliclazide and glipizide should be used, but the longer-acting ones like glibenclamide and chlorpropamide should not be used. Glinides group of OHAs are to be avoided. Glitazones have a low risk of causing hypoglycemia, yet it is better to avoid in the elderly for the risk of fluid retention, increased incidence of bone fractures, and bladder cancer. Metformin and DPP4 inhibitors are relatively safe in older diabetics. SGLT2 inhibitors do not cause hypoglycemia but should be used cautiously in frail older populations for the risk of further weight loss.
- Among the injectables, insulin should be prescribed only after evaluation of administering abilities, regular glucose monitoring, and understanding of hypoglycemia. GLP1 agonists may not increase hypoglycemia risk, but their cost and weight loss limit their use in the elderly diabetic population.
- The non-pharmacological approach comprises proper nutrition therapy, immediate control of fever if present and training of carers for recognition and treatment of hypoglycemia.

Treatment Goals

- Although glycemic targets are based on HbA1c, in the uncommon instances of anemia, polycythemia, hemoglobinopathies, hemodialysis, or recent blood loss or transfusion, this parameter may be misleading.
- Elderly diabetics should be regularly assessed for physical function, cognitive impairment, microvascular complications, frailty, and comorbidities to set the glycaemic targets.
- Elderly diabetics and their caregivers should be assessed for disease managing skills for diabetes care and be given education.
- Elderly diabetics with good quality of life with either none or very mild microvascular complications with a life expectancy of at least 10 to 15 years should have an A1C target of 7 -7.5%.
- Those with diabetes with moderate cognitive impairments, microvascular complications, and comorbid conditions should have an A1C target of 7.5-8.5%.
- The elderly with advanced microvascular complications and /or major comorbid illness and /or life expectancy of fewer than five years may have an A1C target of >8.5%. Such people should be treated only to prevent osmotic symptoms, infection control, or modify cardiovascular risk factors.
- For older adults with type 1 diabetes, continuous glucose monitoring should be considered mainly for those at risk of hypoglycemia, including insulin deficiency necessitating insulin therapy, progressive renal insufficiency, etc.
- For patients receiving palliative and end-of-life care, the focus should be on avoiding hypoglycaemia and symptomatic hyperglycemia while reducing the burden of glycaemic management. Thus, as organ failure develops, several agents will have to be de intensified or discontinued. For the dying patient, most agents for type 2 diabetes may be removed.

Treatment Simplification Regimens

Timely simplification and deintensification of complex treatment regimens in elderly diabetics go a long way in reducing adverse events, improving the compliance and quality of life (QOL) of an individual. Implementing the available screening tools to access the safety of polypharmacy will help the clinician in selecting a regimen which is simple, safe and most beneficial to an elderly diabetic. Based on the overall health status of an elderly patient, the appropriate treatment simplification or deintensification should be done.

A. General

Globally, the burgeoning population of older adults poses diverse health challenges that include medical, cognitive, psychological, social, and financial dimensions, all of which can seriously impact diabetes care. India's population trajectory between the years 2000 and 2050 indicates a 55% increase in total population from 1008 to 1572 million but a 326% increase of 60+ (76 to 324 million) and a 700% increase of 80+ individuals (6 to 48 million)[1257]. The magnitude of diabetes among older adults in India is also enormous, including old and young onset diabetes, which is carried forward to 60+ age. Roughly a quarter of people in their 70s and 80s are diabetic, and in addition, many are in pre-diabetic stage. According to Longitudinal Ageing Study in India (LASI), the self-reported prevalence of diabetes mellitus among Indian adults aged 45-59 was found to be 9% while among the older adults aged 60 and above it was 14%[1258]. In terms of the global diabetes epidemic, India ranks second after China with 77 million people with diabetes. Of these, 12.1 million are aged >65 years, which is estimated to increase to 27.5 million in the year 2045[1259].

Primary care physician needs to realize that majority of older adults in India have financial limitations, are rural based or living under marginalized conditions, and that the advancing age brings about some impairment of cognitive understanding, a fatalistic attitude, and a lack of will and motivation that is enough to interfere with the compliance of medical advice given to him. Further, management of diabetes in old age has to be individualized since the care of older diabetics is complicated by wide heterogeneity among these patients[1260]. Such heterogeneity could be with respect to the level of their physical and mental functioning, expected life expectancies, duration of diabetes, the prevalence of chronic complications, and relative burden of co-morbidities like hypertension, heart disease, stroke, arthritis, cognitive impairment, incident falls, chronic kidney, liver and pulmonary diseases. Economic, social, and emotional deprivation also affects some but not others. Consequences of aging like higher cardiovascular risk, wider glycaemic variability, increased risk of hypoglycaemia, greater deleterious effects of persistent hyperglycaemia, altered pharmacokinetics, and differentials in the type of living arrangement (e. g. with family, living alone, or in old age home) also determine the therapeutic strategy for older diabetics.[1261] In fact, RSSDI determined advancing age as one of the important factors in the patient-centric approach for individualization of diabetic management and included it in their diagrammatic representation termed as RSSDI-ESI Therapeutic Wheel[1262]. In short, management of diabetes in old age demands a rational choice of antidiabetic agents and an easily understood simplified regimen that would achieve the desired glycaemic goals with or without the support of a trained informal or formal caregiver.

Care of diabetes in older adults becomes more difficult in the presence of certain complex clinical conditions, the geriatric syndromes which traditionally comprise the 5 'Is' that is **I**mpaired intellect (confusion, delirium, and dementia), **I**mbalance (with resulting falls and fractures), **I**mmobility (associated with frailty, sarcopenia, and impaired lower extremity performance), **I**ncontinence (multiple etiology) and **I**mpaired vision and hearing. Other common geriatric syndromes include polypharmacy and depression while sleep disorders like insomnia and sleep apnoea have been recently added to the list[1263].

Furthermore, caring for an older diabetic is far more than keeping sugar, lipids, and blood pressure under control. The primary physician also needs to ensure subjective well-being and good mental health for the remaining period of life, especially for an older individual. Ordinarily, many older adults have psychological and social problems, but when it comes to people in their 90s and 100s, many studies have observed that despite declining physical health, nonagenarians and centenarians have better mental health compared to younger adults[1264,1265]. Since better resilience and adaptability attained from their long-standing coping abilities, bonding with family for social support, and connecting with religion are thought to be determinants for better mental health and longer life span, both formal and informal care providers need to build and strengthen these determinants through well-accepted methods in order to preserve a good quality of life for older individuals with diabetes also.

B. Diabetes And Geriatric Syndromes

The phenotype of diabetes in old age is characterized by an increased prevalence of multiple geriatric syndromes. Geriatric syndromes are common clinical conditions that do not fit into specific disease categories but have the substantial quality of life implications for the functionality of the older individuals[1266]. A long list of these syndromes includes cognitive impairment leading to dementia, frailty, and polypharmacy as the common ones, and the last one of these three is described in the chapter on treatment simplification. Others include urinary incontinence, depression, imbalance, and resulting falls while new ones such as sleep disorders comprising insomnia and sleep apnoea have been added to the list[1263].

Most geriatric syndromes complicate the care of older diabetics by interfering with their self-managing abilities and quality of life. General screening by comprehensive geriatric assessment[1267] helps detect not only locomotor, visual, and hearing impairment but also provides early indication for the presence of many geriatric syndromes which can be specifically screened by well-defined tools if necessary.

Neurocognitive decline leading to dementia: Prevalence of irreversible dementias like Alzheimer's and vascular dementia is more common among older diabetics compared to older non-diabetics. Even though good diabetic control is no guarantee against continuing cognitive decline, both poor control and a longer duration of diabetes worsen the cognitive impairment. Yet it is important to screen every older diabetic to detect early cognitive impairment because self-managing abilities to care for diabetes and quality of life will get increasingly compromised with the progression of dementia. Abilities that may be compromised include forgetting to take medicines, meals, and their contents as prescribed or incorrectly calculating or administering the insulin dose. Hindi Mini Mental Status Examination[1268] and Mini-cog examination[1269] are useful for screening for cognitive decline followed by further referral for neuropsychological evaluation if needed. Although uncommon, the primary physician also needs to evaluate older diabetics for reversible dementias such as vitamin B12 deficiency consequent to long-term metformin therapy and chronic hyponatremia.

Frailty: Frailty is an important condition in old age that is characterized by a reduction of physiological reserve and reduction in the ability to resist physical and psychological stressors[1270]. Frailty is associated with weight loss, weakness, exhaustion, decreased physical activity, slowness of gait, and undernutrition. Sarcopenia is a part of frailty and means reduced muscle protein synthesis, a result of lower testosterone and IGF-1 and increased muscle protein breakdown due to chronic hyperglycemia and inflammation and is associated with insulin resistance. Frailty and its risk can be measured[1271,1272]. Management of frailty in diabetes includes optimal nutrition with adequate protein intake combined with an exercise program that includes aerobic, weight-bearing, and resistance training under medical supervision. Weight-reducing anti-diabetic agents should not be used in frail diabetics and staging of frailty (prefrail or frail) should be taken into account while individualizing anti-diabetic therapy for appropriate glycaemic targets.

C. Lifestyle Management

Lifestyle management (LSM) is the fundamental and cost-effective principle of caring for diabetes at all ages and is an essential component of all clinical practice guidelines[1273]. If practiced well, it is always useful in preventing and controlling diabetes and many other lifestyle disorders. LSM is also essential even if diabetes is being pharmacologically treated by blood glucose-lowering agents. Basically, LSM comprises eating right, exercising well, managing stress, sleeping full, accessing regular health care, and resorting to certain miscellaneous steps.

Issue of compliance to LSM among older diabetics

Cognitive and psychological changes of aging associated with a fatalistic attitude and decreased alertness and drive make the older individual less compliant to the advice of a primary physician. This requires a greater listening to older diabetics and their families, holding motivational interviews, careful counselling, encouraging a behavioural change in the patient, and prescribing simple and easily understood treatment. Compliance will also improve if the older adult patient is advised to enhance his cognition through brain challenging activities like new reading, befriending grandchildren, playing puzzles, learning a new skill such as a musical instrument, computer, a language, and through social networking. Health care has evolved from HCPs giving orders to patients, to HCPs educating and working out a compromise with patients. In other words, we have to learn to "wheel and deal" with our patients to find the best compromise for better outcomes[1274].

D. Medical Nutrition Therapy

Over the years the stress was on the control of blood glucose levels by pharmacotherapy which included insulin and OHAs. After realizing that nutrition always plays a vital role in metabolism, the stress is on medical nutrition therapy (MNT) also[1275]. MNT is in fact a component of lifestyle management but given its considerable importance, it has been described here as a separate topic.

Dietary advice should take into account age-related alterations in appetite, taste, smell, and difficulties in chewing, swallowing, or digestion. Comorbidities like obesity, hypertension, and dyslipidaemia and available support system also determine nutritional therapy in the elderly.

46 percent of type 2 diabetes are overweight or obese. With obesity in patients with diabetes, there is an increased risk of hypertension, chronic kidney disease (CKD) cardiovascular disease (CVD). In overweight or obese patients with diabetes, the rate of complications is also higher by 2-4 percent than in the normal population. A 10 percent reduction in body weight significantly reduces the risk factors associated with diabetes. Medical nutritional therapy is most vital in the elderly, especially at the stage of prediabetes and if they are obese[1276].

In Asia, particularly in India, we have a high carbohydrate diet and a high percentage of our energy requirement comes from carbohydrates only. A weight-reducing diet, rich in fibre & complex carbohydrates that are slowly digested, helps in reducing postprandial peaks as well as weight. Food items with a high glycaemic index should be avoided. Meal replacements both partial and full mean replacements are given when the patient is unable to eat properly or has an aversion for food due to reasons including mood swings.[1277]

As far as diet is concerned most elderly diabetics have quantity of protein which is less than one gram per kilogram of their body weight. They have a high carbohydrate diet and generally have a sweet tooth. It is because this reason that their sugar levels swing a lot. The addition of proteins (vegetarian and non-vegetarian) is the best option, but, there are commercially available medical nutrition items that are rich in protein, fortified with vitamins and minerals, and have fibre elements also.[1278]

E. ORAL ANTIDIABETIC AGENTS

From the point of view of management, we divide elderly diabetics into three segments: the fit elderly, the elderly with compromised activities of daily living and/or with comorbidities[1279] and the elderly who are totally dependent upon care givers.

Due consideration is given to disabilities which may be physical, cognitive, or psychological. One must keep in mind the ongoing pharmacotherapy of comorbidities which may raise the issues of polypharmacy[1280], drug interactions and increased adverse drug reactions (ADRs). The physically fit/gainfully employed segment of the elderly are offered treatment with stringent controls while the targets of the elderly with compromised ADL[1281] are liberal.

The management starts with physical check-ups and assessments of certain body functions. Support system, easy regimens & economy always have consideration. Besides the advice on lifestyle, pharmacotherapy with oral antidiabetic drugs (OADs)[1282] is an important part of diabetic management. The following table illustrates the advantages and disadvantages of different OADs,

Table 45: Advantages and Disadvantages of medications

Medication	Advantage	Disadvantage
Metformin	Low risk of hypoglycaemia, cardiovascular benefit, weight neutral/reducing.	Cannot be used in advanced CRF. Increased risk of lactic acidosis in those with renal impairment, heart failure and sepsis. Causes dyspepsia and flatulence.
Sulfonylureas	Potent, economical suitable for those with renal impairment can be added with other OADs.	Hypoglycaemia – especially long-acting, Wight Gain.
Meglitinides	Short-acting, better for PP hyperglycaemia &, and suitable for those with unplanned eating behaviour e.g. geriatric patients[1283].	Risk of hypoglycaemia and weight gain but less than sulfonylureas.
Alpha-Glucosidase Inhibitors	Low risk of weight gain and hypoglycaemia.	Weak hypoglycaemic action, gastrointestinal side effects especially bulky stools.
Pioglitazone	Works as an insulin sensitizer, suitable for those with renal impairment, and less risk of hypoglycaemia.	Fluid retention worsens heart failure, increases fracture risk, and possibly bladder cancer.
DPP-4 Inhibitors	Low risk of hypoglycaemia, weight neutral.	Gastrointestinal side effects, dose mostly needs to be adjusted with renal impairment except in the case of linagliptin. Vildagliptin is not to be used in CLD.
Oral GLP-1 Receptor Agonist (Semaglutide)[1284]	Low risk of hypoglycaemia, and weight loss.	Not suitable for frail elderly.
Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors	Low risk of hypoglycaemia, weight loss & BP Reduction.	Not suitable for frail elderly, increases risk of urinary tract infections, candidiasis & dehydration.

F. INJECTABLES

Insulin and GLP1 receptor agonists are the two classes of injectable therapy options for diabetic patients. In elderly diabetics, drugs with low a risk of hypoglycemia are preferred. Insulin and GLP1RA are potent anti-diabetic drugs giving an HBA1C reduction to the tune of up to 1.5 %. If used with proper caution and monitoring, these agents can offer good glycemic control without hypoglycemia in elderly diabetics. Additionally, GLP1RA offers cardiovascular benefit, renal benefit, and improvement in BP and lipid parameters, especially in overweight or obese elderly diabetics.

INSULIN THERAPY IN ELDERLY DIABETICS:

Apart from conventional NPH and Regular short-acting insulin, we now have newer insulins with smooth glycemic control, which help to reduce glycemic variability and hypoglycemia episodes. At the time of insulin initiation, patient and caregiver education regarding the pen device, administration technique, insulin injection sites, hypoglycemia symptoms, and management is very vital. The cognitive and functional status of the patient should also be considered.

Basal insulins are long-acting insulins like Glargine U100, Detemir, and ultra-long-acting insulins like U300 and Degludeg and offer peakless round-the-clock glycemic control. They are usually given at bedtime. In elderly diabetics, the starting dose should be lesser than the typical 0.2 IU/kg/day. One needs to start with a lower dose and up titrate based on the individualized insulin titration chart. The FPG (fasting plasma glucose) target for the elderly can be between 90—150 mg/dl. If there is a frequent incidence of hypoglycemia, especially nocturnal hypoglycemia, the basal insulin can be shifted to the morning dose (after breakfast)[1285]. If the FPG target stays above the goal, one can increase 2 units of basal insulin. Similarly, if FPG is below the target, can decrease 2 units of basal insulin. The patient needs to be followed up once in 2 weeks.

Prandial insulins are newer ultra short-acting insulins like aspart, glulisine, and lispro which can be used to control prandial peaks. In elderly diabetics with frequent nocturnal hypos, it is better to avoid prandial insulin before dinner. Prandial doses can be given before breakfast and lunch. The prandial glycemic target can be between 180—220 mg/dl based on the overall health status of an elderly diabetic. As with basal insulin, the dose of prandial insulin can be titrated based on pre-meal glucose values. If pre-meal glucose is above 250 mg/dl, 2 units of insulin can be increased, and if it is above 350 mg/dl, an increment of 4 units daily can be done until the glycemic target is achieved[1285]. In case of frequent hypos and if the prandial dose is below 10 IU, other non-insulin drug options should be initiated.

Pre-mix insulins include an NPH and a short-acting prandial component in different compositions like 30/70, 25/75,50/50. Twice daily dosing (before breakfast and dinner) is sufficient, reducing the number of daily injections compared to a basal-bolus regimen. But, there is more glycemic variability and less TIR (time in range) with premix insulins, increasing the chances of hypoglycemia. If there are frequent hypos in elderly diabetics using premix insulin, 70 % of the total premix dose can be given as a single, morning-time basal insulin dose.

GLP1RA THERAPY IN ELDERLY DIABETICS:

Incretin-based therapies including dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists stimulate insulin secretion in a glucose-dependent manner resulting in a lower risk of hypoglycaemia when used as monotherapy or in combination with agents that do not increase insulin levels[1286], and could therefore be a good alternative for the elderly, especially overweight and obese.

GLP-1 receptor agonists have demonstrated pleotrophic benefits in patients with atherosclerotic cardiovascular disease (ASCVD) and those at higher ASCVD risk, and newer trials are expanding our understanding of their benefits in other populations. In a systematic review and meta-analysis of GLP-1 receptor agonist trials, these agents have been found to reduce major adverse cardiovascular events, cardiovascular deaths, stroke, and myocardial infarction to the same degree for patients above and below 65 years of age[1287]**.** While the evidence for this class for older patients continues to grow, there are several practical issues that should be considered for older patients. These drugs are injectable agents, which require visual, motor, and cognitive skills for appropriate administration. Common adverse events with GLP1RA are nausea, vomiting, and diarrhoea. Given the gastrointestinal side effects of this class, GLP-1 receptor agonists may not be preferred in older patients who are experiencing unexplained weight loss.

It has been reported that patients with T2D have a higher incidence of cognitive decline and T2D is associated with an increased risk of dementia and Alzheimer's disease development[1288]. High glucose levels in themselves are also thought to have detrimental effects on the aging brain and may be associated with an increased risk of dementia in populations both with and without diabetes. Conversely, stringent glycaemic control in elderly patients may result in hypoglycaemia, which may also have detrimental effects on cognitive function and cognitive impairment in itself also increases the risk of hypoglycaemia. It is therefore important to consider a treatment regimen that not only is effective in HbA1c reduction but also has demonstrated low incidences of hypoglycaemia.

Dulaglutide, Lixisenatide, and Liraglutide are the three injectable GLP1RA available in India. Semaglutide is the only oral GLP1RA.

Dulaglutide is a human GLP-1 receptor agonist, with a half-life of ~5 days allowing once-weekly dosing. It is administered with a single-use pen with no requirement for reconstitution or dialing of a dose[1289] . It is not renally excreted and pharmacokinetic studies have shown that neither age nor renal function affects its actions, thus no dose adjustment is required in these settings. Starting dose is 0.75 mg subcutaneous after dinner once a week for initial 4 weeks. Then, it can be upitrated to 1.5mg weekly based on the tolerability and GI side effects.

LIRAGLUTIDE: It is a once-daily subcutaneous GLP1RA. The usual starting dose is 0.6mg daily. But, in elderly diabetics, one can start with a lower dose of 0.3 mg and up titrate every 2 weeks based on tolerability. In a study comprising elderly diabetics, liraglutide improved glycaemic control, lipid profile, and visceral obesity for 3 years. In addition, the hippocampal atrophy and arteriosclerosis were not deteriorated, suggesting the possibility of being effective for the prevention of dementia.[1290] In another study, twenty-four weeks of liraglutide treatment was associated with reductions in fat mass and android fat. In addition, to prevent sarcopenia, it preserved the muscular tropism.[1291]

LIXISENATIDE: It is a GLP1RA given once daily. It has a short half-life and is useful as a prandial GLP1RA, generally given before the major meal of the day. The optimum daily dose of Lixisenatide is 20 micrograms subcutaneous. In a meta-analysis conducted on data from older patients (≥65 years) from five of the GetGoal trials, in which patients with T2DM were treated with lixisenatide 20 μg once daily as an add-on to OADs, lixisenatide improved glycaemic control with respect to HBA1C, FPG and PPG.[1292]

G. Hypoglycemia In Elderly

Care of the older adults with diabetes is complicated by their clinical, cognitive and functional heterogeneity. Hypoglycemia is one of the major limiting factors when trying to achieve recommended levels of glycemic control at any age[1293,1294]. The elderly population also has a high prevalence of cardiovascular morbidity which can be aggravated by hypoglycemia. A fine balance needs to be achieved by individualization of therapy so that hypoglycemia can be avoided and simultaneously, the burden of hyperglycemic complications can be reduced.

Hypoglycemia in the elderly is defined as any blood sugar level below 70 mg/dl. Incidence of hypoglycemia in older people (>75 years) with diabetes is difficult to estimate due to the limited number of clinical studies and the lack of standardization in hypoglycemia diagnosis. Tight control of blood sugar can result in undesirable hypoglycemia[1295] which in older patients has a higher risk of poor outcomes due to altered adaptive physiologic responses to low glucose levels[1296,1297].

Hypoglycemia unawareness is also common in older adults and increases the risk of silent hy

hypoglycemia that remains unrecognized[1298] both by symptoms as well as finger stick glucose measurement. Aging modifies the counter-regulatory and symptomatic responses to hypoglycemia. Many hypoglycemic episodes are mild or even asymptomatic and are not likely to be reported. However, a severe single episode of hypoglycemia may result in serious acute consequences such as seizure, coma, and cardiac arrhythmias. It also has a bidirectional relationship with cognitive dysfunction and leads to poor outcomes[1299].

Other devastating complications of hypoglycemia that leads to a decline in quality of life include an increase in falls and fractures, fear of falling, confusion, delirium, and symptoms such as fatigue and dizziness[1300]. Thus, in older adults, it is crucial that individualized care and treatment strategies include early recognition and management of hypoglycemia and in turn, glycemic targets can be adjusted based on the patient's functional, cognitive, and disease status.

Risk factors for hypoglycemia in older people with diabetes include longer duration, insulin treatment and some sulfonylureas, polypharmacy, erratic meals, insufficient carbohydrate intake, renal impairment, liver impairment, cognitive impairment, malabsorption or slowed intestinal absorption and swallowing problems, and last but not the least, it could be blocked PEG tube.

Avoiding medications with a high risk of hypoglycemia is a reasonable first step in the prevention of hypoglycemia. Sulfonylureas especially chlorpropamide and glibenclamide should be avoided in the elderly. Glibenclamide (also known as glyburide) has been classified as a potentially inappropriate medication in older adults by the American Society of Geriatrics[1301] and has been replaced with gliclazide by the World Health Organization in the diabetes section of the list of essential medicines.[1302]

Other drugs that need attention in the elderly are used of glinides and insulin, especially in frail older patients or elderly patients with multiple co-morbidities where their nutrition is poor, they are carer dependent and regular glucose monitoring may not be feasible. Education strategy should be developed for the carer in terms of proper nutrition for the patient and regular monitoring of blood glucose levels. Also, it should be reinforced on each visit for better implementation

Furthermore, HbA1c may be misleading in the elderly population due to anemia, thalassemia, polycythemia, hemoglobinopathies, hemodialysis or recent blood loss[1303,1304] and hypoglycemia may not be recognized.

H. Treatment Goals

Treatment goals for relatively healthy elderly diabetics with good cognitive and physical functioning are same as for young diabetics i.e. HbA1c <7% but for many elderly diabetics, these need to be relaxed i.e. HbA1c 7-8 or even 9%[1305]. The concept of relaxing the goals finds support from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial in which HbA1c of < 6% was associated with increased mortality.[1306]This should not however imply clinical inertia on the part of treating clinicians and desired glycaemic goals at a minimum should avoid the deleterious consequence of persistent hyperglycaemia namely, dehydration, hyperosmolar coma, incontinence, cognitive decline, poor wound healing, sarcopenia, visual disturbances, and poor lower extremity performance. Table 1 summarizes HbA1c-related glycaemic targets for elderly diabetics as per the severity of their cognitive impairment, and physical and functional health[1261].

Table 46: Glycaemic targets for elderly diabetics according to cognitive impairment, and physical and functional health.

Parameter	Category patient one	Category patient two	Category Patient three
Cognitive impairment	Nil	Moderate	Severe
Functional status	Independent	Dependent	Dependent
General Health	Fair	Intermediate	Poor
Physical health Frail Microvascular complications and Comorbidities	 No Minimal Minimal	 Yes Moderate Moderate	 Yes Advanced Advanced
Life expectancy	>10-15 years	<5 years	<5 years
HbA1c target	7-7.5%	7.5-8.5%	>8.5%

Notes: 1. A common goal is to keep glycaemic variability at a minimum to avoid hyper and hypoglycaemia. 2. Cardiovascular risk reduction is a part of diabetic management. Control of hypertension among diabetics is useful[1307]. Statin and aspirin are prescribed on an individual basis and for patients above age 70 or 80, primary prevention with aspirin is not recommended.

I. TREATMENT SIMPLIFICATION REGIMENS

With aging, concomitant diseases and conditions along with diabetes become more frequent. Eventually, the elderly diabetics end up taking multiple daily drugs. Since the complexity of treatment regimens and polypharmacy may interfere with self-caring abilities and lead to serious adverse events, the treatment modification approach should be considered[1308].

Polypharmacy is defined as more than ten medications during hospital admission, or more than five medications at discharge used appropriately based on current evidence-based medicine or the use of inappropriate medications and medications without any clinical benefit[1309]. A study of Swedish elderly found that 39% were taking five or more drugs concomitantly[1310]. Before prescribing any new medication for a condition, we need to understand the goals of the patient, caregiver, and the medication's benefit over risk ratio.

Deintensification or deprescribing refers to decreasing the dose or frequency of administration of a treatment or discontinuing treatment altogether. Simplification and deintensification of complex treatment regimens is recommended in elderly diabetics to reduce the risk of hypoglycaemia and polypharmacy, provided it can be achieved within the individualized A1C target. Treatment regimen simplification results

in fewer administration times, fewer blood glucose checks and decreases the need for calculations (e.g. insulin-carbohydrate ratio calculations).
Implementing the available screening tools to identify and assess the safety of polypharmacy in elderly age groups is the first step in mitigating the risk. The various tools which can be used in various settings include NO TEARS tool[1310], Hyperpharmacotherapy Assessment Tool (HAT)[1310], Beers Criteria[1311], Screening Tool of Older Person's potentially inappropriate Prescriptions (STOPP), Medication Appropriateness Index (MAI)[1312,1313] and Anticholinergic Drug Scale[1314].

Table 47 :Simple therapeutic options for elderly diabetics according to their functional status[1315].

Option	Independent (Category I)	Dependent frail (Category II)	Dependent demented (Category III)
Diet	Restrict carbohydrates	Calories, protein intake should be adequate	Calories should be adequate
Exercise	Muscle strengthening	Muscle strengthening	Normal Activities
BW (body weight) reduction	Healthy BW	No	No
Metformin	1st line	1st line Caution in patients with CKD,CHF, sarcopenia, and GI side effects	1st line Caution in patients with CKD, CHF, sarcopenia, and GI side effects
Sulphonylurea(SU)	2ndline	Alternate 1st line Low dose SU can be used as an alternate 1st line agent in frail patients with metformin intolerance	+/-
Insulin	2ndline	Long acting analog	Long acting analog
Thiazolidinediones	2ndline	+/- To be avoided in patients with H/O fractures, CHF. Spontaneous reports of macular edema were found.	+/- To be avoided in patients with H/O fractures, CHF. Spontaneous reports of macular edema were found[1316].
DPP 4-I	2ndline	+/-	+/-
GLP1-RA	2nd or 3rd line	To be avoided for potential GI side effects and weight loss	+/- Cost is the major factor
Meglitinides	2ndline	+/-	To be avoided in demented patients with erratic eating habits, for fear of hypoglycemia.
AGI	2ndline	To be avoided for potential GI side effects and weight loss	+/-

Although SGLT2 inhibitors do not cause hypoglycaemia, they are avoided in frail elderly for fear of weight loss.
In case of severe/recurrent episodes of hypoglycemia or an increase in glycaemic variability, the insulin regimen to be stopped in frail and demented category patients.
Insulin treatment is one of those antidiabetic agents which has considerable potential to cause hypoglycaemia and add to the complexity of the treatment regimen. The following table gives an algorithm for insulin simplification regimen[1285].

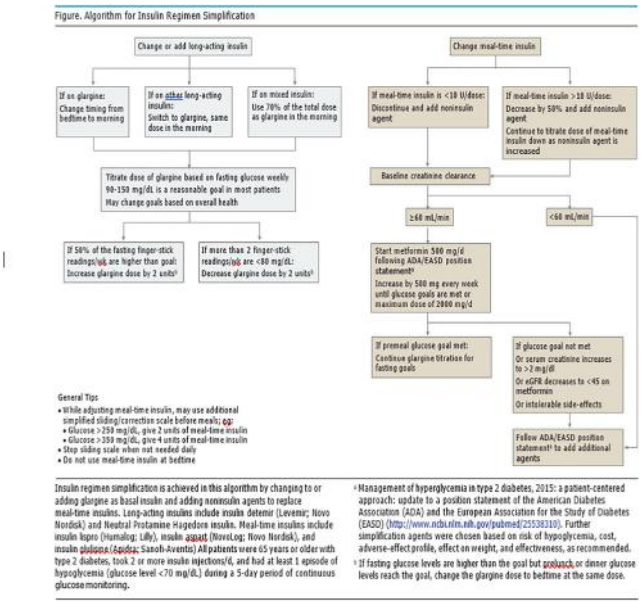


Figure 22: Algorithm for insulin regimen simplification

J. Long-Term Care And The End-Of-Life Care

Long-term care (LT) facilities are scarce in India. Older patients with diabetes who require long-term care are often the residents of old-age homes in this country. Although their categorization in terms of functional severity is variable, when compared to community-dwelling elderly diabetics, old age home resident diabetics are less likely to be independent and fit individuals. Approach to care for diabetes is therefore tailored according to individual patients in old age homes also. Choice of antidiabetic agents and glycaemic targets are set accordingly. More precisely, International Diabetes Federation has identified three groups of older patients with diabetes to facilitate better management. Category 1 includes the functionally independent individuals who do not require support. Category 2 includes functionally dependent individuals and has been divided into frail and those with dementia. Category 3 has been identified as those individuals who are terminally ill and in need of end-of-life care[1317]. Category 3 is described below under end-of-life care.
Long-term care facilities for diabetes care should have an available nurse and be given mandatory sensitization training for LTC staff, caregivers, and the primary physician who is often skilled for only community-dwelling and hospitalized older diabetic patients. The nurse should stress the importance of complying with the prescribed treatment program through effective patient education and emphasize the importance of the effect of blood glucose control on long-term health. LTC patients do not have the benefit of frequent advice from their primary physician who visits them only at fixed intervals e. g. weekly or fortnightly. LTC facilities should have their own points when to suspect emergencies such as hypoglycaemia and acute complications of hyperglycaemia like dehydration and confusion and should be able to provide first aid in such situations. LTC staff should also be able to contact a primary physician for timely advice. Emergency indications for shifting the patient for hospital admission should be clearly laid down. General principles of treatment of older diabetics on long-term care comprise an easily understood simplified treatment regimen which consists of OHAs with low risk of hypoglycaemia, basal insulin if required, and avoidance of undernutrition and weight loss. If pre-meal insulin is needed, it may be better to give it after the meal to match the amount of ingested carbohydrates. The sole use of sliding scale insulin (SSI) should be avoided[1318].
End-of-life care is the approach to a terminally ill patient that shifts the focus of care to symptom control, comfort, dignity, quality of life, and quality of dying rather than treatments aimed at cure or prolongation of life.[1319] Such care is therefore often based on palliative therapy, may be

provided at home, hospice, hospital, or any other setting, and may last for days to weeks[1320] but sometimes may extend to several months.

End-of-life care for people with diabetes should not be viewed as a failure of care, but as a complement to usual diabetes care. The general aims are to consider ethical and legal aspects of care, improve and maintain dignity and quality of life, help the person achieve life goals, manage pain and distressing symptoms, and talk honestly about prognosis and the person's concerns, values, and goals, achieve a dignified death in a place of the person's choosing, and support family and carers.[1321] Principles of end-of-life care for older diabetics include relaxing the goals of blood sugar and blood pressure targets, avoiding hypoglycaemia and undue hyperglycaemia and its effects like dehydration and confusion. Statins can be stopped unless essential. Unnecessary diagnostic procedures should be discouraged and only required doses of OHAs and basal insulin may be administered.

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