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A Practical Approach to the Initiation, Titration and Intensification of Insulin Therapy in Adults with Diabetes in the Indian Context: Recommendations by Association of Clinical Endocrinologists Consensus Group

The grading system used for recommendations:

The grading system uses A, B, C, or E to show the evidence level that supports each recommendation.

- A — Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered
- B — Supportive evidence from well-conducted cohort studies
- C — Supportive evidence from poorly controlled or uncontrolled studies
- E — Expert consensus or clinical experience

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ABSTRACT

Insulin therapy is critical for people with type 1 diabetes (T1D). Although oral antidiabetic drugs (OADs) remain the mainstay of treatment for people with type 2 diabetes (T2D) in the early stages, insulin therapy becomes essential as the disease progresses to sustain life. Whilst there are guidelines and consensus statements from reputed institutions and medical bodies pertaining to diabetes mellitus (DM), there is not a dedicated guideline or consensus statement that is based on an evidence-based grading system that deals exclusively with the "Practical Approach to the Initiation, Titration and Intensification of Insulin Therapy in Adults with Diabetes in the Indian Context",

guiding general physicians and general practitioners. Hence, this consensus statement uses the modified Delphi method.

The Association of Clinical Endocrinologists is a non-profit, non-commercial body registered in India, that serves as a platform for like-minded Endocrinologists who aspire to work for the cause of the science of Diabetes and Endocrinology, its utility and application for the betterment of the health of the people and the country. The authors request the readers to please do not confuse this Association of Clinical Endocrinologists with the American College of Endocrinology/ /American Association of Clinical Endocrinologists (ACE/AACE) of the United States of America (USA).

Keywords: insulin therapy, diabetes mellitus, hyperglycemia, hypoglycemia, type 1 diabetes (T1D), type 2 diabetes (T2D)

Introduction

Diabetes mellitus (DM) is a chronic disease that affects 537 million people worldwide [1]. Globally, 150–200 million individuals depend on insulin, but this number is probably underestimated [2]. Insulin therapy is critical for people with type 1 diabetes (T1D). Although oral antidiabetic drugs (OADs) remain the mainstay of treatment for people with type 2 diabetes (T2D) in the early stages, insulin therapy becomes essential as the disease progresses to sustain life [3]. In India, it is estimated that approximately 4 out of every 10 people with T2D use insulin, either alone or in combination with OADs [4].

Rationale

The vast majority of the people with DM are managed by general practitioners and family physicians, most of them practicing in areas with less-than-ideal healthcare facilities in India. Whilst there are guidelines and consensus statements from reputed institutions and medical bodies pertaining to DM, there is not a dedicated guideline or consensus statement that deals exclusively with the "Practical Approach to the Initiation, Titration and Intensification of Insulin Therapy in Adults with Diabetes in the Indian Context", guiding general physicians and general practitioners. Hence, this consensus statement uses the modified Delphi method.

Methodology

The current analysis used a three-step modified Delphi method to establish the consensus. Delphi approaches are organized group communication methods where professionals assess complicated issues with inadequate and ambiguous knowledge through an iterative procedure. The distinguishing characteristic is that each new questionnaire includes the aggregated group responses from earlier ones, allowing the experts being questioned to review and, if necessary, revise their conclusion statements [5]. In the last few decades, the Delphi techniques have played a crucial role in the development of best practice guidelines utilizing collective intelligence in situations when research is scarce, ethical, and logistically challenging, or the data is contradictory. However, much variation has been seen in attempts to evaluate the quality standard of Delphi investigations, and the details of the methodology are typically ambiguous [6]. Thorough use of scientific research methods, such as the Delphi Panel approach, enables high-quality, scientific expert surveying [7].

There are many forms of Delphi techniques such as the modified Delphi, policy Delphi, and the real-time Delphi [8].

Modified Delphi method

The modified Delphi technique involves gathering information initially using questionnaires and then conducting a formal in-person meeting, that maximizes the advantages [9].

The insights or expert opinions for the current analysis were sought using a 3-step modified Delphi method to enable members of the Association of Clinical Endocrinologists to pool their knowledge and develop recommendations that would facilitate a general physician or general practitioner to address various challenges and barriers and that may aid in proper utilization of insulin therapy in India.

This modified Delphi method comprised 2 email-based questionnaire rounds followed by a consensus physical meeting to allow direct interaction between the experts in the final round, which allowed panel members to clarify their points from the previous rounds and also present arguments to justify their points of view (Fig. 1).

The initial stage was the development of recommendation statements following a comprehensive literature review using PubMed and other online resources for clinical studies, existing guidelines, review articles, consensus statements, and national and international standards on insulin therapy in adults with diabetes. The relevant data was retrieved and reviewed, recommendation statements were developed and compiled into a Microsoft Excel sheet.

The process of developing the recommendations

Consensus statements by highly reputed medical bodies like the American Diabetes Association (ADA)

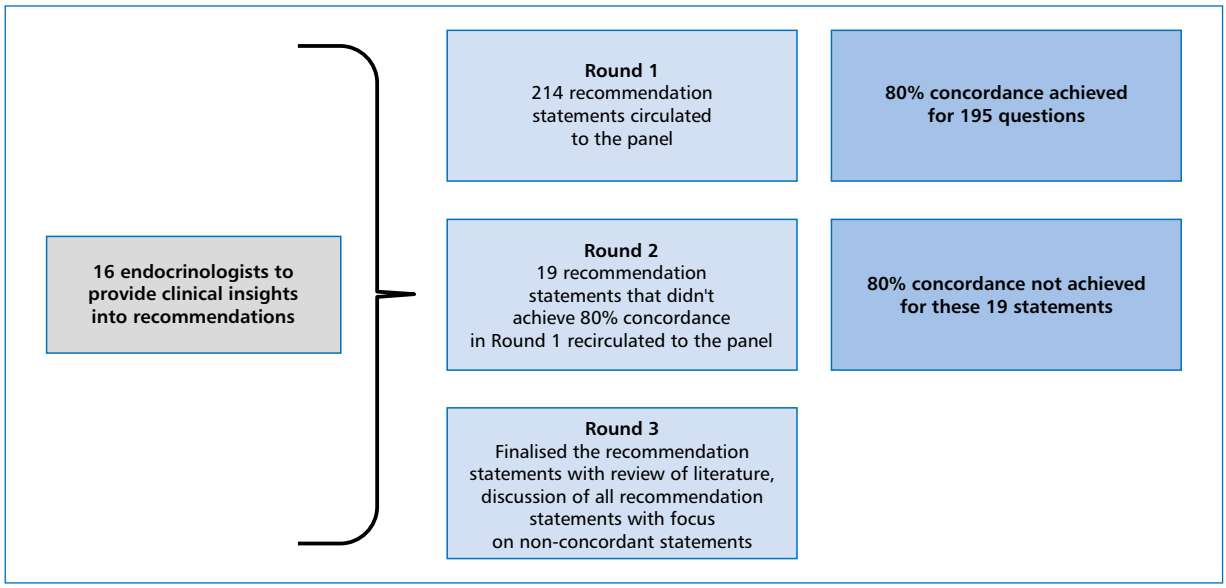

Figure 1. The Modified Delphi Technique Followed

may not suit the Indian milieu due to a variety of reasons including practicality, affordability and the healthcare ecosystem being completely different in India compared to the Western world. While taking the ADA, National Institute for Health and Care Excellence (NICE), European Association for the Study of Diabetes (EASD), The International Society for Pediatric and Adolescent Diabetes (ISPAD), American Association of Clinical Endocrinologists (AACE) guidelines and other peer-reviewed evidence-based guidelines and consensus statements into consideration, the expert panel comprising 16 practicing Endocrinologists from the Association of Clinical Endocrinologists has drafted new recommendations with specific consideration for the Indian milieu keeping in mind the resources available to the general physician or a general practitioner.

Round 1

The recommendation statements were circulated to the panel members through email along with an explanation of the analysis, objectives, and instructions. The questionnaire was presented in a tabular format with columns beside the statements for addition of responses. The experts had to choose "Yes" for "Agree" or" "No" for "Disagree" for each statement and were free to add comments and suggestions in the specified column if required. Anonymity of the answers and comments was maintained all through the process. Statements with at least 80% agreement were considered to have reached concordance and those that did not reach concordance were modified as per the panel's inputs and recirculated in Round 2.

Round 2

The statements that did not reach concordance in Round 1 were circulated among the experts by email. The responses were collected and analyzed in the same manner as in Round 1. Statements not reaching 80% concordance were retained for discussion in Round 3. In the current analysis, 19 statements did not reach 80% concordance which were brought for further discussion to Round 3.

Round 3

Round 3 was a direct interaction round among the experts in person with one member acting as the facilitator in a physical meeting. The panelists were encouraged to discuss the statements until an agreement was reached to modify, eliminate, or retain the statement in the recommendations.

Statistical methods

The responses obtained for each statement were subjected to descriptive statistics, i.e., percentage of response to each consensus statement. 80% agreement for each consensus statement was considered as a standard to be included as a recommendation and statements that did not achieve 80% agreement were recirculated for further discussion and were accepted with iterations.

In the current analysis, of 214 recommendation statements circulated through email in Round 1, 80% concordance was achieved for 195 recommendation statements. Therefore, the remaining 19 recommendations were recirculated in Round 2 but, could not achieve 80% concordance. Hence, a Round 3, physical meeting was conducted with the experts to resolve and obtain consensus on these 19 recommendations, along with all other recommendations.

Need for insulin

Insulin therapy is crucial for people with T1D because the hallmark of the condition, the beta-cell function is nearly absent or diminished. Insulinopenia can cause hyperglycemia, tissue catabolism, hypertriglyceridemia, ketoacidosis, and other metabolic disturbances. For the first six or seven decades following the discovery of insulin, severe metabolic decompensation was avoided with once- or twice-daily injections. However, over the past three decades, evidence has shown that a more intensive insulin regimen, such as multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII) via an insulin pump, offers the best compromise between effectiveness and safety for people with T1D [10]. The Diabetes Control and Complications Trial (DCCT) demonstrated that MDI of intensive therapy with short-acting (regular) and intermediate-acting human insulins or CSII decreased glycated hemoglobin (HbA1c) and were linked to better long-term outcomes [11].

People with T2D who fail to achieve or maintain HbA1c levels over time, even with multiple OADs, will eventually require insulin therapy [12]. However, it is equally crucial to make sure that insulin is started right away once the best combinations of OADs have failed to control blood glucose levels.

Healthcare providers (HCPs) should refrain from using insulin as a threat, a sign of failure, or a punishment, and instead should regularly and objectively explain to people the progressive nature of T2D. Educating to self-titrate insulin doses based on blood glucose monitoring (BGM) improves glycemic control in people with T2D who are initiated on insulin [13]. Structured comprehensive education on diet, hypoglycemia prevention and treatment, self-monitoring of blood glucose (SMBG), and other topics are crucial in any person using insulin [10].

Most guidelines advise people with high HbA1c levels at the time of presentation to begin short-term insulin therapy as soon as possible [10, 14, 15]. According to landmark trials from the previous decade, intensive glycemic control should be practiced in the early stages of diabetes, preferably within the first four years of diagnosis [16]. The traditional practice of delaying insulin therapy until a sustained inability of dietary changes and oral medications to achieve glycemic control has been changed in the past ten years to include insulin therapy much earlier, frequently in conjunction with OADs or glucagon-like peptide 1 receptor agonists (GLP-1RA). In people with T2D, the decision to use injectable therapy is influenced by clinical, pharmacological, and psychosocial factors [14]. In the Indian context, it is also important to consider factors like price, quality, cold chain maintenance, and ongoing availability of insulin preparations and delivery devices [14].

Indications of insulin

Some of the indications of insulin include people with T1D, newly diagnosed T2D with HbA1c > 10%, or catabolic/osmotic symptoms, when oral antidiabetic medications are contraindicated or failed to achieve goals, and need for flexible therapy, in persons with acute illness or surgery, pregnancy, glucose toxicity [3].

Recommendations

Indications of insulin

A. In people with T1D. **A**

B. Individuals with newly diagnosed T2D with HbA1c > 10% or catabolic/osmotic symptoms. **B**

C. People with T2D who are unable to achieve glycemic targets with optimal OADs and GLP1-RAs, or cannot tolerate current OADs, or those who need more flexible therapy. **B**

D. When adequate glycemic control is not achieved in people with myocardial infarction, stroke, or decompensated hepatic or renal insufficiency, or those who had major surgery. **B**

E. In individuals with T2D and acute illness/infection or sepsis. **B**

F. People with glucose toxicity. **B**

G. In hospitalized people with diabetes, if clinically appropriate. **B**

H. In people with stress/drug/steroid-induced hyperglycemia, post-transplant hyperglycemia, diabetes ketoacidosis (DKA)/hyperglycemic hyperosmolar state (HHS)/lactic acidosis. **B**

I. Individuals with T2D who are planning pregnancy, during pregnancy, and lactation. **B**

J. People with uncontrolled diabetes (persistent HbA1c level remains above the set target despite other antidiabetic drugs). **B**

K. Individuals with secondary diabetes. **B**

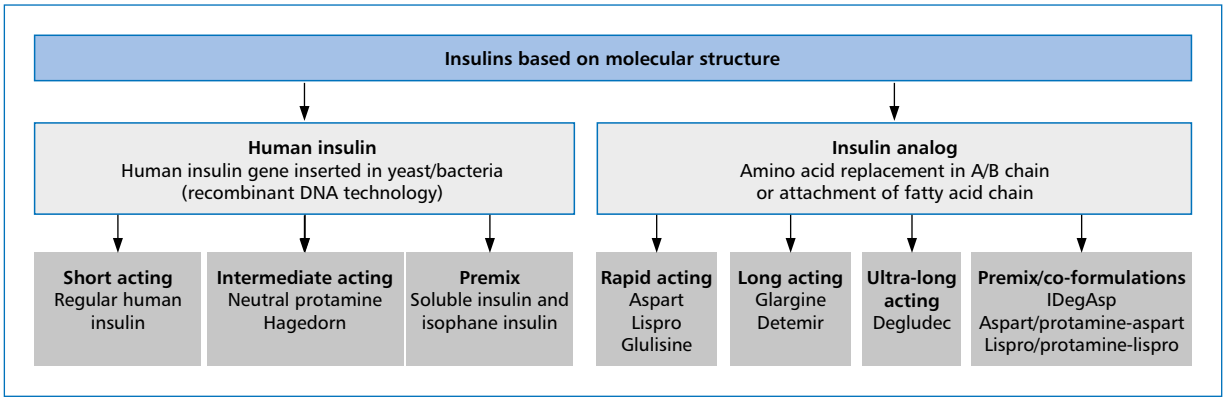

Figure 2. Classification of Insulin (Adapted from [10])
DNA — deoxyribonucleic acid; IDegAsp — insulin degludec + insulin aspart

Classification of insulins

Based on their molecular structure, insulins are classified as human insulins and insulin analogs (Fig. 2) [3]. The insulin that is currently used is recombinant insulin, which is either directly derived from native human insulin or created by structurally altering the amino acid sequence of the insulin molecule (insulin analog). The main differences between human insulin and insulin analogs are in the pharmacokinetic parameters and propensity for adverse effects. When regular human insulin is injected subcutaneously (SC), it takes some time for it to break down into its monomer form and enter the bloodstream. Because of this, regular human insulin frequently fails to control postprandial glycemic excursions and tends to result in delayed hypoglycemia. The use of insulin analogs and their combinations significantly reduces these issues [17].

There are three characteristics of insulin that are relevant in clinical use [18]:

- **onset of action:** the length of time that insulin takes to reach the circulation and begin lowering blood glucose is referred to as the onset;
- **peak time of action:** peak time is when the insulin is at its maximum strength in lowering blood glucose;
- **duration of action:** duration is the amount of time that insulin keeps lowering blood glucose.

Human insulins

Human insulins are manufactured by using recombinant deoxyribonucleic acid (DNA) technology. Human insulins are classified as [3]:

A. Short-acting — human soluble insulin (regular)
B. Intermediate-acting — neutral protamine Hagedorn (NPH)
C. Premix-mixtures of regular and NPH insulin in 25/75, 30/70, and 50/50 proportions

The onset, peak, and duration of action of different kinds of human insulins are summarized in Table 1.

Insulin analogs

Insulin analogs were developed by modifying the amino acid sequence for better management of fasting plasma glucose (FPG) and postprandial plasma glucose

Table 1. Different Types of Human Insulins (Adapted from [19] and [20])

Human insulin types	Onset	Peak	Duration	Examples
Short-acting (regular) [19]	30–60 minutes	2–4 hours	5–8 hours	Humulin® R Insuman® R Actrapid®
Intermediate-acting [19]	2–4 hours	4–12 hours	12–24 hours	NPH
Premix human insulins [20]	30 minutes	2–8 hours	Up to 24 hours	Mixtures of regular and NPH insulin in 25/75, 30/70, and 50/50 proportions

NPH — neutral protamine Hagedorn

Table 2. Different Types of Analog Insulins Available in India (Adapted from [19], [20] and [21])

Analog insulin type	Onset	Peak	Duration
Ultra-rapid-acting insulin (faster aspart) [19]	10–20 minutes	1–3 hours	3–5 hours
Ultra-rapid-acting insulin lispro [21]	15–18 minutes	1–2 hours	~ 4 hours
Rapid-acting analog (RAA) insulin (Insulin aspart, insulin glulisine, insulin lispro) [19]	15–35 minutes	1–3 hours	3–5 hours
Long-acting analogs (LAA)			
Glargine [19]	2–4 hours	8–12 hours	22–24 hours
Detemir [19]	1–2 hours	4–7 hours	20–24 hours
Ultra-long-acting analogs (ULAA)			
Glargine U300 [19]	2–6 hours	Minimal peak	30–36 hours
Degludec [19]	30–90 minutes	Minimal peak	> 42 hours
Pre-mix analog preparations			
Biphasic IAsp [21]	10–20 minutes	1–4 hours	Up to 24 hours
70% aspart protamine, 30% aspart			
50% aspart protamine, 50% aspart			
Biphasic lispro [21]	15–30 minutes	1–3 hours	12–24 hours
75% lispro protamine, 25% lispro			
50% lispro protamine, 50% lispro			
IDegAsp co-formulation [21]	10–20 minutes	1–2 hours	> 24 hours
70% degludec, 30% aspart			

IDegAsp — insulin degludec + insulin aspart

(PPG) levels with minimal hypoglycemic risk. Based on their pharmacokinetic characteristics, insulin analogs are classified as rapid-acting insulin analogs (RAA), long-acting insulins (LAA) analogs, ultra-long-acting insulin analogs (ULAA), and pre-mix analog preparations [10].

The onset, peak, and duration of different kinds of analog insulin are summarized in Table 2.

Insulin regimens

Initiating and titrating insulins in people with T1D

It is of paramount importance to acknowledge that the choice of insulin regimen and the initiation, titration, and intensification doses of any insulin regimen instituted for any person with diabetes are based on multiple factors including the type of diabetes, HbA1c, current blood glucose readings, age, body weight, pregnancy and lactation, comorbidities, concurrent medication use, hypoglycemia risk, knowledge and skills of the HCP, the person's lifestyle, awareness, affordability and choices of the person and the limitations of the healthcare system [10, 19]. The insulin regimens and doses suggested in this guideline for initiation, titration, and intensification are a rough guide only and due clinical discretion of the HCP is mandatory whilst individualizing insulin treatment.

Basal-bolus regimen (BBR) is the most preferable regimen in people with T1D [22]. Insulin regimens should be customized to the individual's age, general health, lifestyle, treatment objectives, hypoglycemia awareness status, medication adherence, and ability to self-manage. Social and economic factors should also be considered [10].

Basal insulin dosage is estimated based on weight and is normally initiated at 0.1 to 0.2 units/kg body weight/day [10] and then up-titrated based on glycemic values, with typical doses ranging from 0.2 to 1.0 units/kg body weight/day. Short-acting insulins should be added for PPG control [13, 15]. Patient education programs such as dose adjustment for normal eating (DAFNE) which enable those with T1D to understand the principles of carbohydrate (CHO) counting and self-adjust insulin doses need to be encouraged [23]. Premix insulin regimens are sub-optimal but can be used where a person with T1D prefers these over BBR [10].

Initiating and titrating insulins in people with T2D

The initial regimen of insulin therapy is based on the person's age, clinical features, glucose profile, risk of hypoglycemia, cost, and person's preference. Either basal insulin or premix insulin can be considered as an initial insulin regimen in people with T2D [12]. When FPG is high, consider initiating insulin therapy with

basal insulin. When both FPG and PPG are high, one may consider initiating insulin therapy with premix insulin [10]. BBR is the initial insulin regimen in acutely unwell and hospitalized people with T2D, women with T2D planning pregnancy when other regimens do not achieve optimal glycemic control, and in people with challenging lifestyles [15]. Analog insulins may be preferred over human insulins as they possibly reduce the risk of hypoglycemia and are flexible to use [10]. However, economic considerations must be taken into account.

Structured education and training should be provided for all insulin users regarding storage, administration, SMBG/continuous glucose monitoring (CGM), dose adjustment, hypoglycemia prevention, and treatment strategies. Concordance with insulin usage should be evaluated at regular intervals [10].

Insulin doses should be titrated regularly at least once a week, but more frequently if required [24]. FPG levels and PPG levels should be aimed at 80–130 mg/dL and 140–180 mg/dL respectively in the majority of people with T2D [24, 25]. These targets can be individualized, based upon the risk of hypoglycemia and the need for glycemic control. Initially, titration should be done to control FPG, followed by PPG for prandial insulin with the highest glycemic fluctuation, in a sequential order [25].

Insulin intensification should not be delayed for individuals not meeting treatment goals. Therapy intensification is recommended for those whose HbA1c is still uncontrolled following basal insulin introduction and titration [10]. The advantages and disadvantages of various insulin regimens are discussed below in Table 3 [26].

Table 3. Insulin Regimens: Advantages and Disadvantages (Adapted from [26])

Types of insulin regimen	Advantages	Disadvantages
Basal insulin	Effective and safe It is simple and easy for early facilitation of insulin Potentially less weight gain Low risk of hypoglycemia Useful for symptom relief if tight control is not a major issue	Some individuals may not achieve glycemic targets The regimen doesn't offer optimum control of post-prandial hyperglycemia
Premix/co-formulation	Better PPG control It is more effective in lowering HbA1c when compared to basal insulin alone Simple for the person to understand than BBR	Less flexibility (i.e., a person is unable to adjust the bolus or basal component of the insulin independently) Fixed daily routine about lifestyle, CHO content, and meal timing is required There is a time delay of injection with conventional mixture (need to inject 20–30 minutes before a meal)
Basal plus	Better flexibility It is comparable to other conventional approaches in terms of glycemic control It offers the additional advantages of fewer hypoglycemic events Personalization of therapy, and a simple self-management algorithm for titration	Weight gain Some may need progression to BBR Careful patient evaluation and scheduling is necessary due to the complicated nature of this regimen
Basal-bolus	Potential for better metabolic control if used optimally Closely mimics normal physiology Potential for the better control of FPG and PPG Potential for a better lifestyle choice Offers optimum flexibility in terms of diet and activity	Requires multiple insulin injections More complicated to support and teach Needs CHO counting Risk of hypoglycemia and weight gain Needs better patient cooperation Requires more frequent glucose monitoring

BBR — basal-bolus regimen; CHO — carbohydrate; FPG — fasting plasma glucose; HbA1c — glycated hemoglobin; PPG — postprandial plasma glucose

Recommendations

Insulin therapy in people with T1D

A. For individuals with T1D, BBR of basal and prandial insulin or CSII has proven to be an effective and safe therapy. **A**

B. BBR insulin therapy is considered as the standard regimen for the management of T1D. **A**

C. Basal insulin dosage is estimated based on weight and is normally initiated at 0.1 to 0.2 units/kg body weight/day and then up-titrated based on glycemic value, with typical doses ranging from 0.2 to 1.0 units/kg body weight/day. **A**

D. Short-acting insulins to be added for PPG control. **A**

E. Premix insulin regimens are sub-optimal but can be used where a person with T1D prefers these over BBR. **C**

F. Individuals with T1D should be instructed on how to adjust prandial insulin dosages to CHO intake, basal insulin as per FPG levels, and planned physical activity. **B**

G. Patient education programs such as DAFNE which enable people with T1D to understand the principles of CHO counting and self-adjust insulin doses need to be encouraged. **B**

Insulin initiation in people with T2D

A. HCPs should refrain from using insulin as a threat or as a sign of failure or punishment. **B**

B. Consider insulin therapy when a person fails to achieve or maintain HbA1c levels after administration of three OADs/GLP1-RA or if the person is intolerant to any individual agent or combination of agents. **A**

C. Despite the availability of several new oral medications, insulin should never be postponed if HbA1c levels remain high, since insulin has a far greater ability to decrease blood glucose than other medications. **A**

D. Involvement of a person with diabetes, and their carer is important in making a decision regarding the therapeutic choice of regimen, preparation, and delivery device. **B**

E. Metformin, GLP1-RA, sodium-glucose cotransporter-2 inhibitors (SGLT2i), dipeptidyl peptidase-4 inhibitors (DPP4i), and alpha-glucosidase inhibitors (AGIs) can be continued upon insulin initiation (unless contraindicated or not tolerated) for ongoing glycemic and metabolic advantages. Sulfonylureas are usually discontinued after insulin initiation with other insulin regimens, but they are usually used along with basal insulin regimen. **B**

F. Pioglitazone can be used with insulin therapy with extreme caution considering the weight gain and water retention side effects. **C**

G. The initial regimen of insulin therapy is based on the type of diabetes, the person's age, clinical features, glucose profile, risk of hypoglycemia, cost, and personal preference. **B**

H. Either basal insulin or premix insulin can be considered as an initial insulin regimen in people with T2D. When FPG is high, consider initiating insulin therapy with basal insulin. When both FPG and PPG are high, one may consider initiating insulin therapy with premix insulin. **B**

I. BBR is the initial insulin regimen in acutely unwell and hospitalized people with T2D, women with T2D planning pregnancy when other regimens do not achieve optimal glycemic control, and in people with challenging lifestyles. **B**

J. Analog insulins may be preferred over human insulins as they possibly reduce the risk of hypoglycemia and are flexible to use. However, economic considerations must be taken into account. **B**

K. Individuals initiating insulin therapy and their caretakers should be educated about SMBG/ /CGM, as well as hypoglycemia prevention and treatment strategies. **A**

L. Structured education and training should be provided regarding dose adjustments, administration, storage, and other practical aspects of insulin. **A**

M. Insulin intensification should not be delayed for individuals not meeting treatment goals. **A**

N. Concordance of insulin usage should be evaluated at regular intervals. **E**

O. Review the ratio of basal and prandial insulin periodically to optimize blood glucose levels. **C**

Insulin titration in people with T2D

A. Insulin doses should be titrated regularly at least once a week. but more frequently if required. **A**

B. FPG levels and PPG levels should be aimed at 80–130 mg/dL and 140–180 mg/dL respectively. These targets can be individualized, based upon the risk of hypoglycemia and the critical need for glycemic control. **A**

C. Initially, titration should be done to control FPG, followed by PPG for prandial insulin with the highest glycemic fluctuation, in a sequential order. **B**

Simplifying insulin initiation in the context of Indian realities

Since T2D is a progressive condition, most people will eventually require treatment intensification. This generally entails gradually introducing a new glucose-lowering medication or moving to a more complex insulin regimen [27]. Complex treatment regimens may be more physiological and flexible but might result in an increased risk of hypoglycemia and a high treatment load, which can have a poor influence on both therapeutic adherence and overall quality of life (QoL). Treatment simplification strives to decrease individual treatment burdens while maintaining therapeutic efficacy and safety. Although there is evidence that simplifying insulin treatment can result in efficient glycemic control without jeopardizing therapeutic efficacy or safety, it is not commonly implemented in clinical practice [27].

The term "simplification" is seen to be the most appropriate to describe reducing the number of insulin injections (including termination) and modifying the treatment plan to each individual's circumstances. Therefore, individuals with T2D who are on a complex insulin therapy regimen should be assessed frequently and insulin regimen simplification should be considered with the goal of improving clinical outcomes like risk of hypoglycemia and QoL [10, 27].

Barriers to insulin initiation

Even though the majority of practitioners consider the start of insulin therapy to be crucial to the management of T2D, many view it as the "last option" and report that their patients are hesitant to accept this treatment [28]. The unwillingness to initiate insulin therapy might be due to physician-related, patient-related, or system-related barriers [28].

Physician-related barriers may include their lack of knowledge of updated guidelines, experience of insulin therapy, beliefs and attitudes towards insulin and diabetes management, side effects of insulin therapy (e.g., hypoglycemia and weight gain), and perceptions of patients' attitudes towards insulin therapy (patient's adherence, and wish to prolong non-insulin therapy) [29].

Patient-related barriers include fear of needle and injection phobia, hypoglycemia and weight gain, negative effects of therapy on occupation and social life, the difficulty of administering injections, perceptions of personal failure in self-management, and the effectiveness of therapy [29].

System-related barriers include limited access to education, limited training of providers in injection techniques, overburdened workload among providers, and poor adherence [30].

Recommendations

A. A simplified and personalized insulin regimen that can be easily titrated and intensified improves patient compliance. **B**

B. Structured education is essential to address both clinician and patient barriers regarding the initiation and intensification of insulin therapy. **E**

C. Structured patient education is an ongoing process starting from initiation and continuing through titration and intensification of insulin treatment. **B**

Basal insulin regimen

Basal insulin includes human NPH insulin, LAA, ULAA, and also continuous RAA insulin delivery via an insulin pump [10]. Basal insulin regulates hepatic glucose production by maintaining a steady quantity of insulin in the background [24]. Presently, the Indian market offers NPH, glargine U100 and U300, detemir, and insulin degludec. Basal insulin analogs have a longer duration of action with flatter, more constant plasma concentrations and activity profiles than NPH insulin [10]. LAA, such as glargine is currently the most widely used basal insulin after NPH. LAA is followed by the ULAA basal insulin analogs, such as insulin degludec and U300 glargine [10].

ULAA has documented a lower incidence of overall and nocturnal hypoglycemia, a longer duration of action, and a stable profile in comparison to LAA basal insulin analogs (glargine and detemir). Despite offering an equivalent level of glycemic control, LAA basal insulin analogs have been found to have a lower risk of hypoglycemia than NPH insulin [31]. Advantages of ULAA such as U300 glargine and degludec include a flat peakless profile, low variability, once-daily (OD) dosing, variable time of administration, and a reduced risk of nocturnal hypoglycemia [24].

Initiation of basal insulins

It is recommended to initiate basal insulin dosage at 6–8 units/day or 0.1 to 0.2 units/kg body weight/day if HbA1c is ≤ 8% and 8–10 units/day or 0.2 to 0.3 units/kg body weight/day if HbA1c is > 8% (Fig. 3) [32]. Lower and higher doses [33] than these may be needed based on individual clinical case scenarios.

Titration

The active titration period is defined as the time period when the physician adjusts the basal insulin

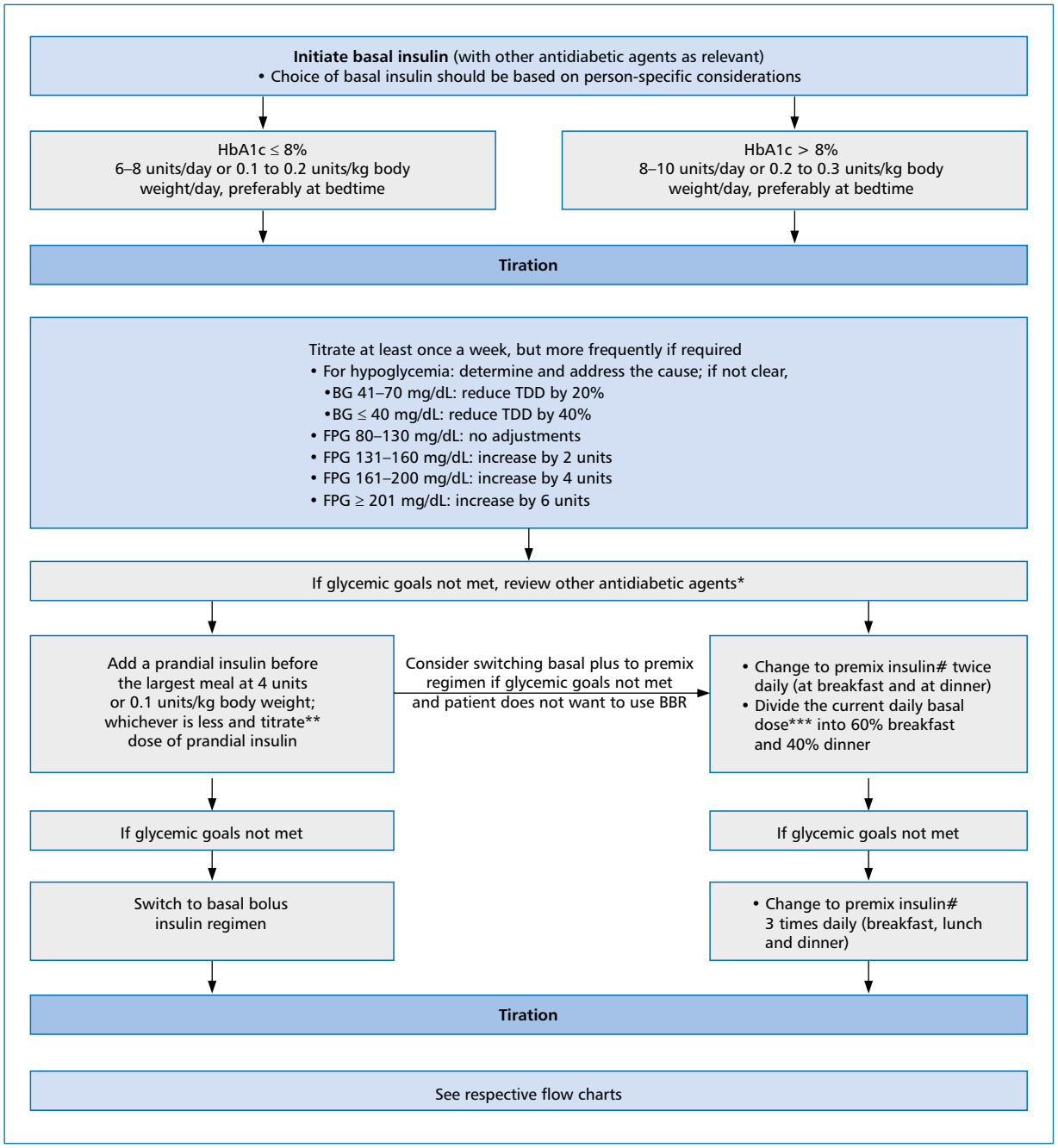

Figure 3. Steps for Initiation, Titration, and Intensification of Basal Insulin
*If not on antidiabetic agents like GLP-1RA, SGLT-2i, DPP4i consider these agents; **See Figure 5 for titration of bolus insulin; ***Total basal + bolus dose if converted from basal plus regimen; #Premix/co-formulation
BG — blood glucose; BBR — basal-bolus regimen; DPP4i — dipeptidyl peptidase-4 inhibitors; GLP-1RA — glucagon-like peptide 1 receptor agonist; FPG — fasting plasma glucose; HbA1c — glycated hemoglobin; , SGLT-2i — sodium glucose co-transporter 2 inhibitors; TDD — total daily dose

dose. This period usually lasts up to 12 weeks after starting insulin therapy. Ideally, the maximum reduction in HbA1c and FPG should be achieved by week 12 after starting insulin therapy, and a minimal reduction should be seen after 12 weeks [34].

The recommended target for titration is FPG of 80–130 mg/dL usually. It is recommended to titrate the dose at least once a week, but more frequently based on FPG [24, 25]. The dose can be modified based on the lowest/mean value of the three most recent FPG values [24]. The dose may be reduced by at least 20% for individuals reporting hypoglycemia (< 70mg/dL) [32] unless there is an identifiable and modifiable one-off cause for that episode of hypoglycemia. Insulin therapy should be intensified, in case they fail to achieve glycemic goals even after optimal dose titration. In the Indian context, this regimen may be a simple and effective method for most people. Where possible, the insulin dose can also be titrated 2 units every 3 days [24, 32]. Upon titration, if FPG is 80–130 mg/dL, no adjustments are recommended. If FPG is 131–160 mg/dL, 161–200 mg/dL, ≥ 201 mg/dL it is recommended to increase the basal dose by 2 units, 4 units, and 6 units respectively [24, 32]. Consider reviewing other OADs and GLP-1RA, during the titration if these haven't been optimized already.

If the glycemic goals are not met after optimizing OADs, either add 1 prandial insulin before the largest meal at 4 units or 0.1 units/kg body weight, whichever is less, i.e., change to the basal plus regimen, or opt for premix/co-formulation insulin twice daily (BID) (at breakfast and dinner) and divide the current basal dose into 60% at breakfast and 40% at dinner [24]. If the glycemic goals are not met by premix or co-formulation insulin BID, change to premix/co-formulation insulin thrice daily (TID) (breakfast, lunch, and dinner). If the glycemic goals are still not met, consider switching to BBR [10].

Recommendations

A. It is recommended to initiate basal insulin dosage at 6–8 units/day or 0.1 to 0.2 units/kg body weight/day if HbA1c is ≤ 8% and 8–10 units/day or 0.2 to 0.3 units/kg body weight/day if HbA1c is > 8%. **B**

B. The recommended target for titration is FPG of 80–130mg/dL. **A**

C. It is recommended to titrate the dose at least once a week, but more frequently based on FPG. **A**

D. It is recommended to modify the dose based on the lowest/mean value of the three most recent FPG values. **E**

E. It is recommended to reduce the dose by at least 20% for individuals reporting hypoglycemia (< 70mg/dL) unless there is an identifiable and modifiable one-off cause for that episode of hypoglycemia. **B**

F. Insulin therapy should be intensified, in case person fail to achieve glycemic goals even after optimal dose titration. **B**

G. Prandial insulin can be added to basal insulin with the largest meal of the day, to make it basal plus. **B**

H. Insulin premix regimen can be considered as an option for intensification, in lieu of basal or basal plus insulin regimens if targets are not met. **B**

I. Intensification strategy can be based upon various factors such as type of diabetes, dietary pattern, lifestyle, weight gain, the person's age, clinical features, glucose profile, risk of hypoglycemia, personal choice and cost. **C**

Premix regimen

Once daily premix/co-formulation insulin regimen

Premix insulin therapy is appropriate for people who are unable to calculate CHOs or have constant eating patterns and a predictable lifestyle. To attain the target HbA1c values, insulin therapy can be started with premix insulin OD and then intensified to BID or TID [35].

Premix insulins are indicated in people with T2D who did not attain glycemic targets with OADs or basal/basal plus insulin, and people with T1D (need to initiate with at least BID premix) [35].

A. Initiation

If HbA1c ≤ 8, OD premix insulin can be initiated at 6–8 units with the largest meal of the day.

B. Titration

The recommended target for titration is a pre-meal value of 80–130 mg/dL [24, 32]. The dose can be titrated at least once a week, but more frequently based on pre-dinner or pre-breakfast values [34]. It is recommended to modify the dose based on the lowest/mean value of the three most recent pre-breakfast/pre-dinner glucose values [34]. Premix analogs can be given immediately before or after the meal, while human premix insulins need to be given 30 minutes before the meal [20]. For individuals reporting hypoglycemia (< 70 mg/dL), it is recommended to reduce the dose by 20% unless there is an identifiable and modifiable one-off cause for that episode of hypoglycemia

[10, 32]. Premix analog insulins/co-formulations have a lower risk of hypoglycemia, and better safety, flexibility, and convenience compared to human premix or co-formulation [10].

Breakfast dose adjustments are titrated based on pre-dinner values. No dose adjustments are recommended if the pre-dinner values are ≤ 140 mg/dL. If pre-dinner values are between 141–180 mg/dL, can increase the dosage by 2 units. It is recommended to increase the dosage by 4 units and 6 units if the pre-dinner values are between 181–220 mg/dL and ≥ 221 mg/dL respectively.

Dinner dose adjustments are titrated based on pre-breakfast values. No dose adjustments are recommended if the FPG values are between 80–130 mg/dL. If FPG values are between 131–160 mg/dL, it is recommended to increase the dosage by 2 units. It is recommended to increase the dosage by 4 units and 6 units if the FPG values are between 161–200 mg/dL and ≥ 201 mg/dL respectively.

Recommendations

A. It is recommended to start premix insulin with 6–8 units OD with the largest meal of the day if HbA1c ≤ 8%. **B**

B. The recommended target for titration is a pre-meal value of 80–130 mg/dL. **A**

C. It is recommended to titrate the dose at least once in a week but more frequently based on pre-dinner or pre-breakfast values. **A**

D. It is recommended to modify the dose based on the lowest/mean value of the three most recent pre-breakfast/pre-dinner glucose values. **E**

E. Premix analogs can be given immediately before or after the meal, while human premix insulins need to be given 15 minutes before the meal. **E**

F. It is recommended to reduce the dose by 20% for individuals reporting hypoglycemia (< 70 mg/dL) unless there is an identifiable and modifiable one-off cause for that episode of hypoglycemia. **B**

G. Premix insulin can be administered BID or TID as a part of intensification. **E**

H. Premix analog insulins/co-formulations have a lower risk of hypoglycemia, safety, flexibility, and convenience compared to human premix or co-formulation. **C**

Twice daily premix/co-formulation insulin regimen

A. Initiation

When BID premix/co-formulation is necessary and insulin is initiated in an insulin-naïve person, it is recommended to initiate BID premix/co-formulation at 12–16 units or higher doses and divide the total daily dose (TDD) as 60% at breakfast and 40% at dinner.

B. Titration

The recommended target for titration is a pre-meal value of 80–130 mg/dL. It is recommended to titrate the dose at least once a week, but more frequently based on pre-dinner and pre-breakfast values [24]. The dose can be modified based on the lowest/mean value of the three most recent pre-breakfast/pre-dinner glucose values. It is recommended to reduce the dose by 20% for individuals reporting hypoglycemia (< 70 mg/dL) unless there is an identifiable and modifiable one-off cause for that episode of hypoglycemia [10, 24].

Breakfast dose adjustments are made based on pre--dinner values. No dose adjustments are recommended if the pre-dinner values are ≤ 140 mg/dL. If pre-dinner values are between 141–180 mg/dL, one may increase the breakfast dosage by 2 units. It is recommended to increase the dosage by 4 units and 6 units if the pre-dinner values are between 181–220 mg/dL and ≥ 221 mg/dL respectively.

Dinner dose adjustments are titrated based on pre-breakfast values. No dose adjustments are recommended if the FPG values are between 80–130 mg/dL. If FPG values are between 131–160 mg/dL, it is recommended to increase the dosage by 2 units. It is recommended to increase the dosage by 4 units and 6 units if the FPG values are between 161–200 mg/dL and ≥ 201 mg/dL respectively.

If the glycemic targets are not met and the target HbA1c is not reached even after 3 months, one may intensify premix/co-formulation from OD to BID and BID to TID. While intensifying from OD to BID, it is recommended to increase the TDD by 10% and split it into 60% at breakfast and 40% at dinner, and keep it titrating till glucose values are achieved.

Recommendations

A. When BID pre-mix/co-formulation is necessary for an insulin-naïve person (HbA1c > 8%), it is recommended to start with 12–16 units or higher doses if appropriate and divide TDD as 60% at breakfast and 40% at dinner. **B**

B. The recommended target for titration is a pre-breakfast value of 80–130 mg/dL and pre-dinner values ≤ 140 mg/dL. Breakfast insulin dosage is adjusted based on pre-dinner glucose values and dinner insulin dosage is adjusted based on pre-breakfast glucose values. **A**

C. It is recommended to reduce the dose by 20% for individuals suffering from hypoglycemia (≤ 70 mg/dL) unless there is an identifiable and modifiable one-off cause for that episode of hypoglycemia. **B**

Thrice daily premix/co-formulation insulin regimen

A. Initiation

While intensifying from BID to TID, if pre-dinner values are above target, one may initiate 4–6 units at lunch and reduce the morning dose by 10% [35]. Whenever TID premix is considered, it is recommended to prefer 50/50 over 30/70 premix insulin (Fig. 4) [14].

B. Titration

The recommended target for titration is a pre-meal target of 80–130 mg/dL. For titrating TID premix/co-formulation, breakfast insulin dosage is adjusted based on pre-lunch glucose values, lunch insulin dosage is adjusted based on pre-dinner values, and dinner insulin dosage is adjusted on FPG values [24].

It is recommended to titrate the dose at least once a week, or more frequently based on fasting, pre-lunch, and pre-dinner values. The dose can be modified based on the lowest/mean value of the three most recent pre-breakfast/pre-lunch/pre-dinner values [24].

Recommendations

A. It is recommended to add 4–6 units at lunch when converting a premix BID regimen to a premix TID regimen and reduce the breakfast dose by 10%. Whenever TID premix is considered, it is recommended to prefer 50/50 over 30/70 premix insulin. **B**

B. Down-titration of the morning dose to 10% of TDD may be needed after adding the lunch dose. **B**

C. The recommended target for titration is a pre-meal target of 80–130 mg/dL. Breakfast insulin dosage increase is adjusted based on pre-lunch glucose values; lunch insulin dosage is adjusted based on pre-dinner values; and dinner insulin dosage increase is adjusted on FPG values. **A**

D. It is recommended to titrate the dose at least once a week, but more frequently if required, based on fasting, pre-lunch, and pre-dinner values. **A**

E. It is recommended to modify the dose based on the lowest/mean value of the three most recent pre-breakfast/pre-lunch/pre-dinner values. **B**

Basal plus insulin regimen

A "basal plus" method is the addition of a single prandial insulin injection to the already used basal regimen before the main meal or the meal commensurate with the highest PPG [36]. This regimen has proven to be an effective way to intensify insulin therapy before implementing a full BBR or in lieu of BBR [10, 14, 32]. Careful patient evaluation and scheduling are necessary due to the complicated nature of this regimen. This regimen is best suited for those with T1D and T2D who are younger, extremely motivated, energetic, and have diverse eating habits [37]. Basal plus regimen is a step-by-step approach to basal insulin intensification that can lead to BBR prescription if necessary.

A. Initiation

This can be initiated by starting a short-acting insulin at a dose of 4 units or 0.1 unit/kg body weight (whichever is lower), with the main meal of the day, while continuing the existing basal insulin [10].

B. Titration

The recommended target for basal dose titration is FPG of 80–130 mg/dL. The prandial insulin dose is recommended to be titrated once a week, but more frequently if required, based on the 2-hour PPG value [24]. For individuals reporting hypoglycemia (< 70 mg/dL), it is recommended to reduce the dose by at least 20% [10, 32].

Recommendation on titration of basal insulin

FPG (mg/dL)	Dose adjustments (units)
80–130	0
131–160	+ 2
161–200	+ 4
≥ 201	+ 6

Recommendation on titration of prandial insulin

PPG (mg/dL)	Dose adjustments (units)
≤ 180 mg/dL	0
181–200	+ 1 to 2
201–220	+ 2 to 3
≥ 221	+ 3 to 4

Recommendations

A. When intensification with basal plus is necessary, start one injection at mealtime with the largest meal of the day. **B**

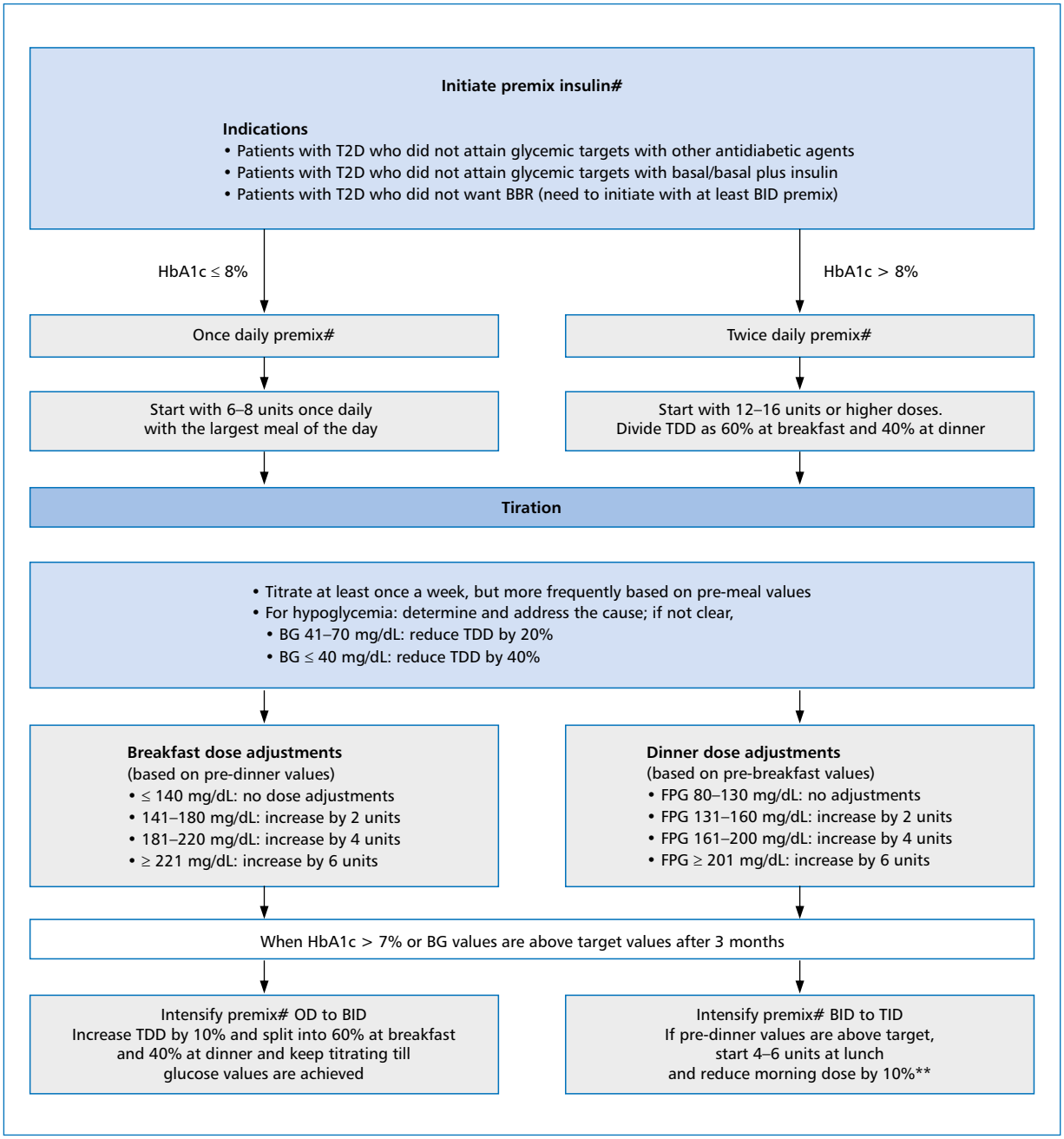

Figure 4. Steps for Initiation, Titration, and Intensification of Premix/Co-Formulation Insulin
When BID changed to TID consider changing 30/70 premix to 50/50 premix
**Breakfast insulin dosage is adjusted based on pre-lunch glucose values; lunch insulin dosage is adjusted based on pre-dinner values; and dinner isulin dosage is adjusted based on FPG values; #Premix/co-formulation
BG — blood glucose; BBR — basal-bolus regimen; BID — twice-daily; FPG — fasting plasma glucose; HbA1c — glycated hemoglobin; OD — once-daily; T2D — type 2 diabetes; TDD — total daily dose; TID — thrice-daily

B. Starting dose is 4 units or 0.1 unit/kg body weight, whichever is lower. The prandial insulin dose is recommended to be titrated at least once a week, but more frequently if required, based on the 2-hour PPG value. **A**

C. The recommended target for basal dose titration is FPG of 80–130 mg/dL. **A**

D. It is recommended to reduce the dose of basal/bolus by at least 20% for individuals suffering from hypoglycemia (< 70 mg/dL) depending on the time of hypoglycemia-FPG/PPG respectively, unless there is an identifiable and modifiable one-off cause for that episode of hypoglycemia. **B**

E. Basal plus regimen is a step-by-step approach to basal insulin intensification that can lead to BBR prescription if necessary. **A**

Basal-bolus regimen

Basal-bolus regimen is used when basal insulin alone does not achieve target glycemic control. It almost replicates the natural production of insulin by the pancreas. A long-acting insulin is used as basal insulin to control fasting/pre-meal glucose and short-acting insulin as bolus is administered with each meal to control PPG excursions. To achieve the desired level of glycemic control with this regimen, frequent and active SMBG, understanding of the insulin-CHO ratio and correction factors, and titration of the insulin are required [37].

BBR is indicated in people who fail to achieve glycemic targets with basal/basal plus/premix/co-formulation insulin regimens with or without OADs, people with T1D, [10] secondary diabetes, and those with frequent hypoglycemia with premix/co-formulation insulins.

A. Initiation

To initiate this regimen in insulin naïve people, it is recommended to calculate the total insulin dose as 0.5 units/kg body weight for people with T1D [38] and 0.2–0.3 units/kg body weight for people with T2D [32]. It is recommended to divide TDD into 40% as basal insulin given usually at bedtime and 60% as prandial insulin divided into 3 doses at each meal.

To initiate this regimen in people switching from other insulin regimens (basal/basal plus/premix/co-formulation), an increase in TDD by 10% may be considered and then, divide TDD into 40% as basal insulin given usually at bedtime and 60% as prandial insulin divided into 3 doses at each meal (Fig. 5).

B. Titration

The recommended target for titration of the prandial component is a 2-hour PPG value of ≤ 180 mg/dL. The recommended target for titration of basal components is a FPG value of 80–130 mg/dL. It is recommended to titrate the dose at least once a week, or more frequently based on FPG and PPG values for basal and bolus insulins respectively [24].

It is recommended to address the FPG first, this is typically best accomplished with a bedtime basal insulin dosage ('Fix Fasting First') [39].

It is recommended to modify the dose based on the lowest/mean value of the three most recent FPG values [24]. A lower starting dose, slower titration, and higher glucose targets may be recommended for those people at higher risk of hypoglycemia.

The TDD of basal and/or prandial insulin can be reduced by 20% if the blood glucose level is consistently < 70 mg/dL. FPG and PPG readings are considered for dose adjustments so that basal and prandial insulins are adjusted accordingly.

While titrating basal insulin, no dose adjustments are recommended if the FPG levels are between 80–130 mg/dL. If the FPG values are between 131–160 mg/dL, it is recommended to increase the dosage by 2 units, and if FPG values are between 161–200 mg/dL and ≥ 201 mg/dL, increase the dosage by 4 units and 6 units respectively.

While titrating prandial insulin, no dose adjustments are recommended if the 2h PPG levels are ≤ 180 mg/dL. If the PPG values are between 181–200 mg/dL, it is recommended to increase the dosage by 1–2 units. It is recommended to increase the dosage by 2–3 units and 3–4 units if the PPG values are between 201––220 mg/dL and ≥ 221 mg/dL respectively.

Recommendations

A. It is recommended to calculate the total insulin dose as 0.5 units/kg body weight for people with T1D and 0.2–0.3 units/kg body weight for people with T2D. **B**

B. 40% of the TDD to be given as basal insulin as a single dose usually at bedtime. **B**

C. 60% of the TDD to be given as prandial insulin divided as 3 doses at each meal. **B**

D. The recommended target for titration of basal component is a FPG value of 80–130 mg/dL. **B**

E. The recommended target for titration of the prandial component is a 2-hour PPG value of ≤ 180 mg/dL. **B**

F. It is recommended to titrate the dose at least once a week, or more frequently based on FPG and PPG values for basal and bolus insulins respectively. **B**

G. It is recommended to address the FPG first. This is typically best accomplished with a bedtime basal insulin dosage ('Fix Fasting First'). **B**

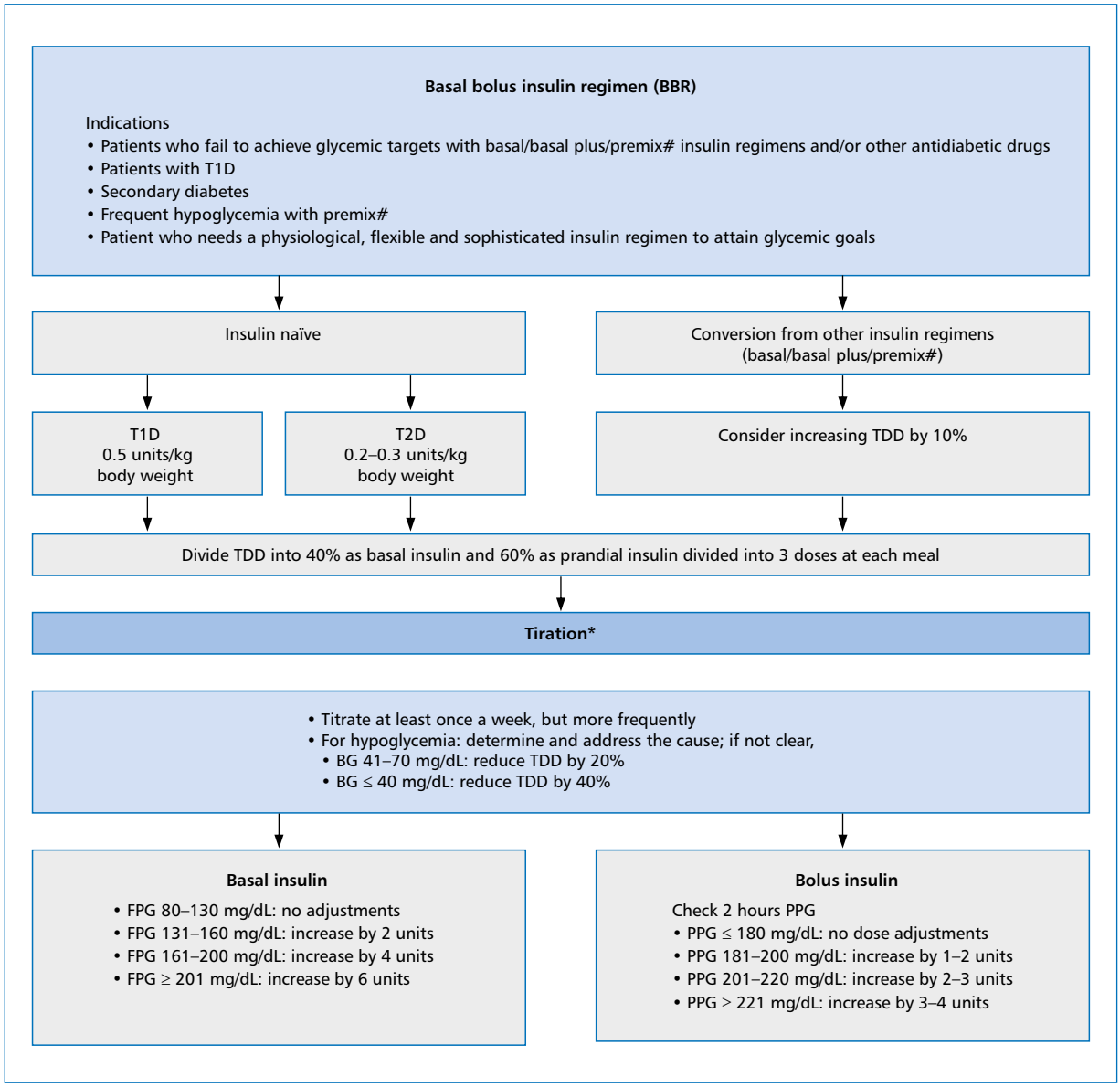

Figure 5. Steps for Initiation, Titration, and Intensification of Basal-Bolus Insulin
#Premix/co-formulation; *Dose adjustments need consideration of FPG and PPG values, and basal and prandial insulins are adjusted accordingly; BG — blood glucose; FPG — fasting plasma glucose; PPG — postprandial plasma glucose; T1D — type 1 diabetes; T2D — type 2 diabetes; TDD — total daily dose

H. It is recommended to modify the dose of the basal and prandial insulins (bolus doses) based on the lowest/mean value of the three most recent FPG and relevant PPG values respectively. **E**

I. A lower starting dose, slower titration, and higher targets may be recommended for those people at higher risk of hypoglycemia. **C**

Insulin injection technique

Insulin must be administered properly into the appropriate tissue. Although insulin therapy remains the cornerstone of diabetes management, the skill of injecting insulin is not properly understood by many users and even some HCPs. A proper insulin injection technique should consider appropriate injection sites in the body, injection technique, rotating injection sites,

caring of injection sites, and avoiding intramuscular (IM) insulin administration [40].

Insulin delivery devices

A. Insulin syringes

Insulin syringes were the most popular method for delivering SC insulin. The capacity and type of the syringe is chosen based on the dose and concentration of insulin [40]. Other things to consider when choosing an insulin syringe are needle gauge and needle length, as larger needles increase the risk of IM injections [40].

Insulin syringes may be utilized for insulin delivery considering individual and carer preferences, insulin type, dosage regimen, cost, and dexterity. It is advised not to draw insulin with syringes from insulin cartridges/penfills/pens. The best suggested needle length for an insulin syringe is 6 mm [40]. Needles longer than 6 mm for adults or teenagers are not advisable.

Glass syringes should be replaced with plastic fixed-needle syringes that have less dead space and are intended for single use [41]. Many people reuse insulin needles for a variety of reasons, including cost considerations [40]. The manufacturers do not advise this, as there is a link between lipohypertrophy (LH) and needle reuse. The reuse of needles triggers more pain at the injection site.

B. Insulin pens

Insulin pens are prefilled cartridges of insulin that are devised to make injections easier and more flexible. They eliminate the need to extract insulin from a vial; they may be especially beneficial for insulin delivery when away from home, at school, or on a holiday. While using a pen, it is recommended to count from 1 to 10 before removing the needle, to allow time for any air bubble in the cartridge to expand [19]. Wherever possible, usage of insulin pens is recommended over syringes due to convenience, accuracy of dosage, and safety reasons [42].

There are two main categories of insulin pens: disposable and durable. Disposable insulin pens are prefilled with insulin and are thrown away once they are empty [40]. Insulin pens are only permitted for single-person usage. Individuals should never share their insulin pen cartridges with others so as to avoid the risk of biological contamination in the pen cartridges even if a new needle is used [40].

Insulin pens may be considered as a better option than syringes for people with vision impairment or dexterity issues, children, and elderly people to ease the administration of accurate insulin doses. A 4 mm needle is recommended to be used with pens [40]. When compared to the traditional vial/syringe, the scale on insulin pens is simpler to read.

Disposal

Proper disposal of used insulin vials and syringes is mandatory [15, 19]. Ideally, they should be disposed off in sharps containers that have been carefully labeled and are available for sale in pharmacies and a few diabetes centers. Ideally, the needle may be taken out and rendered unusable using specialized needle clippers (like a safe clip) [19]. Syringes with removed needles can be disposed off in tins or opaque plastic containers [19]. People with diabetes and their family members who improperly dispose sharp objects are at risk of needle-stick injuries among themselves, domestic waste handlers, and the community [43]. HCPs ought to take responsibility for educating people about proper disposal and spreading awareness about it. In case of unavailability of sharp bins, needles should be gathered in a sturdy cardboard or glass container, or used soft drink tin, sealed and marked, and sent to the nearest healthcare facility.

According to a research study in New Delhi, 84.1% of people with diabetes put sharps right into their residential garbage containers [44]. The results of a recent worldwide injection technique questionnaire (ITQ) study, which included 7.6% of subjects from India, revealed that a significant amount of used sharps still end up in household garbage [45]. Improper disposal techniques resulted in sharps injuries in the community in 8.6% of the overall population [45].

Insulin concentrations

Insulins are available in the strengths of U40 and U100 concentrations in India. U100 means 100 units of insulin in 1 mL. U200 and U300 insulins are also available, but exclusively in the form of a pen. To minimize dosage problems, it is mandatory to use a U40 syringe for U40 insulin and a U100 syringe for U100 insulin vials [40].

Intravenous (IV) syringes should never be used for insulin delivery [40]. The date of opening the vial should be recorded with a black/marker pen, and it should be utilized usually within 28 days [46].

Most of the concentrated insulins, such as lispro U200, regular insulin U200, and regular insulin U500, were developed to overcome severe insulin resistance and satisfy the demands of a substantial supply of insulin. Concentrated U300 basal insulin glargine offers the advantages of low injection volume leading to less pain, low variability, and lesser risk of overall hypoglycemia, including nocturnal hypoglycemia, and can be prescribed as an alternative to U100 basal insulin [47].

Injection sites

The abdomen, thigh, and buttocks were suggested as the most common injection sites [10]. After the in-

sulin has been injected, the person should count slowly till 10 and then withdraw the needle from the skin [3]. Insulin administration through SC tissue is most often employed in ambulatory persons. Additional methods include IV infusion which is only used in cases of DKA, HHS, when insulin administration is indicated in a nothing-by-mouth (NBM) scenario, in the emergency and intensive care unit (ICU) setting, to name a few [40]. IM insulin is almost never advised, due to erratic absorption, and risk of hypoglycemia and may be rarely considered in exceptional circumstances only [48].

Injection site rotation

Injections should be switched between sites systematically to maintain a healthy injection site so as to improve insulin absorption and lower the risk of LH [40]. LH occurs when there is an accumulation of SC fat at the injection site as a result of insulin's adipogenic effects [40]. LH can cause irregular insulin absorption, increased glycemic variability, and unexplained hypoglycemia episodes. It manifests as soft or rubbery fatty swellings at the site of repeated insulin injections [40].

An alternative efficient strategy to rotate the injection site is to split the injection site into quadrants (abdomen) or halves (thighs, and buttocks). After using one quadrant or half for a week, switch to the next one in either a clockwise or an anticlockwise direction. Adolescents should use the abdominal area most often [40].

The distance between the new injection site and the previous injection site should be at least 1 cm [48]. Avoid injecting in areas with infections, edema, or LH. Injection sites should be examined by the HCPs at least once a year and preferably at every visit [48]. Education regarding correct injection site rotation and how to spot and stay away from areas of LH should be provided to individuals and/or their carers [48].

Needle length

Ideally, a 6 mm needle should be used with syringes and a 4 mm needle should be used with pens [40, 43]. In teenagers or adults who are slender to normal weight, a syringe needle injection should always be administered into a raised skinfold at 90° [40].

Ideally insulin needle should be used only once. If reusing the needle is intended, which is not ideal, it must be thoroughly recapped after each use. The needle should never be cleaned or washed and needles should be changed after a maximum of 3–4 uses, to avoid needle infection [3]. It is recommended to follow the correct site rotation policy.

Storage and transport

Insulin should preferably be stored in a cool (< 30°C) and dark environment, as per the manufacturer's recommendations [40]. The ideal temperature for transporting insulin should be between 2 and 8°C [3]. Insulin vials can be kept in a pot with sand if refrigeration is not available [49].

Insulins' potency and efficiency can be diminished when they are exposed to direct sunlight or high temperatures. Excessive agitation should be avoided to avoid potency loss, clumping, frosting, or precipitation. As a result, it is crucial to maintain the temperature while transporting [40, 49].

If refrigeration is not available, insulin should be kept cool for example, in an earthenware pot of water (inside a ziplock plastic bag), thermos flasks, or ice bags. Various unconventional methods of insulin storage include pot-in–pot refrigerators or the Zeer pot, mud pots, goat skin pots filled with water, vegetable gourds filled with water, and buckets filled with wet sand [50]. Regular insulin should not be used if it appears hazy. Cloudy insulin should not be used if it cannot be re-suspended [40, 49]. Regardless of where it is kept, opened insulin has a shelf life of 28 days and it needs to be discarded after that [46]. Before administering insulin, it should be taken out of the refrigerator and allowed to reach room temperature. 'Never freeze insulins' is the dictum [3, 40].

Insulin stability

Used vials can be stored in a clean plastic box and out of direct sunlight for six weeks at room temperature (20–25°C), or four weeks if the temperature rises to 30°C. Insulin can degrade or be converted to larger molecular weight components if it is stored at higher temperatures [43]. According to Pendsey et al., the insulin that has not been refrigerated may be thermostable for up to two months, and in some cases up to four months [51].

The steps for using an insulin syringe and vial

- Wash hands thoroughly.
- Check the expiry date and type of insulin.
- Bring insulin to room temperature.
- If the insulin is cloudy, roll the bottle between your hands until it is uniformly mixed.
- Extract air into the syringe equal to the dose of insulin to be taken.
- Pierce the rubber stopper of the insulin vial in the middle at a 90° angle and push the air in.

- Holding the bottle upside down, extract the dose into the syringe.
- Ready for injection. Place the syringe on the table carefully without letting the needle touch the surface.
- Select the site and it should be completely dry before injecting.
- To inject insulin, slowly push the needle through the skin fold.
- Count to 10 (more in case of large dose) before pulling the needle out. Release the skin fold.
- Clip the syringe needle with a safe clip. Dispose the needle safely.

Recommendations

Insulin delivery devices

A. Wherever possible, use insulin pens over syringes due to convenience, accuracy of dosage, and safety reasons. **B**

B. Insulin pens are usually preferable for individuals using BBR insulin therapy. Insulin syringes may be utilized for insulin delivery considering individual and carer preferences, insulin type, dosage regimen, cost, and self-management capacities. **C**

C. Insulin pens should be considered for people with dexterity issues or vision impairment to facilitate accurate dosing and administration of insulin. **C**

D. Pen devices improve patient safety, convenience, and adherence. **B**

Insulin concentrations and strength

A. Concentrated U300 basal insulin offers the advantages of low injection volume leading to less pain, low variability, and lesser risk of hypoglycemia, including nocturnal hypoglycemia, and can be prescribed as an alternative to U100 insulin. **C**

B. In those people requiring very high dosage of insulin, pump therapy may be considered as an option, if affordable. **A**

C. High-concentration short-acting insulin can be administered in people who have severe insulin resistance and need higher doses of insulin in a single injection. **C**

D. Use U40 syringe only for U40 insulin and U100 syringe only for U100 insulin vials. **A**

E. Do not draw insulin with syringes from insulin cartridges/penfills/pens. **A**

Insulin transport and storage

A. The manufacturer's recommended storage guidelines included in the package inserts should be followed. **E**

B. Insulin can be transported from a healthcare institution to an individual's home without the use of an ice pack if no excessive temperature changes are anticipated. It is recommended to transport insulin on an ice pack if there is any doubt about whether it will be exposed to extreme temperatures (> 30°C). **A**

C. Insulin vials can be transported by keeping insulin in a pot with sand or in an earthenware pot of water (inside a ziplock plastic bag) if a refrigerator is unavailable. **B**

D. Insulin must not be exposed to heat or sunlight. Excessive agitation should be avoided to prevent clumping, frosting, precipitation, or loss of potency. **A**

E. While going on a holiday, insulin pens and vials may be carried appropriately using insulin storage boxes sold in some pharmacies or at least in a thermos flask with ice, or in a proper clean container if the outside temperature is > 30°C. Never leave insulin in a locked vehicle with the windows closed. **B**

F. If regular insulin seems cloudy, it shouldn't be used. Insulin that is hazy and cannot be resuspended should not be used. **A**

G. Vials that have been opened can be stored in a refrigerator (2–8°C) or at a controlled ambient temperature. Regardless of where it is kept, opened insulin has a shelf life of 28 days and it needs to be discarded after that. Before administering insulin, it should be taken out of the refrigerator and allowed to reach room temperature. Never freeze insulins. **A**

Injection sites

A. Abdomen, thigh, and buttocks are the recommended injection sites. **A**

B. IM insulin injections should not be given. **B**

C. After the insulin has been injected, the person should count slowly till 10 and then withdraw the needle from the skin. **B**

Injection site rotation

A. Systematic switching of injections from one site to another helps to keep injection sites healthy, optimize insulin absorption, and minimize the danger of LH. **A**

B. The distance between the new injection site and the previous injection site should be at least 1 cm. **A**

C. The injection site should be reviewed by HCPs at every possible opportunity. **A**

Needle length

A. Ideally, a 4 mm needle is recommended with pens and a 6 mm needle with syringes. **A**

B. In extremely lean and elderly people, a skinfold is required when using 5 and 6 mm needle. **B**

C. A shorter needle should be inserted perpendicularly to the skin surface. **A**

D. Ideally, insulin needle should be used only once. **B**

E. If reusing the needle is intended, it must be thoroughly recapped after each use. The needle should never be cleaned or washed. If in case the needle is reused for any reason, change needles after a maximum of 3–4 uses to avoid needle infection. **C**

F. Correct site rotation policy must be followed. **A**

Needle stick injuries

A. If bleeding and bruising occur often, the injection method should be carefully evaluated, and the occurrence of a coagulopathy, usage of anticoagulant or antiplatelet drugs should be investigated. **B**

Disposal of needles

A. Ideally, safe disposal of needles is done in a sharps bin with the help of local healthcare facilities or appropriate authority. **A**

B. In case of unavailability of sharps bins, needles should be gathered in a sturdy cardboard or glass containers, or used soft drink tins, sealed and marked, and sent to the nearest healthcare facility. **C**

Hypoglycemia

Hypoglycemia is a major challenging event during the glycemic management of a person with diabetes. Level 1 hypoglycemia is termed when blood glucose is ≥ 54 mg/dL and < 70 mg/dL. Level 2 hypoglycemia is when the blood glucose is < 54 mg/dL and level 3 hypoglycemia is when a severe incident is defined by changed mental or physical status needing help for treatment of hypoglycemia (Fig. 6) [52].

Hypoglycemia symptoms include shakiness, anger, disorientation, tachycardia, and hunger. For people with diabetes, hypoglycemia symptoms can be uncomfortable or scary. Hypoglycemia at level 3 might result in unconsciousness, seizures, coma, or even death. At each visit, doctors should assess the person's risk of hypoglycemia, especially if they are on insulin [53].

It is worth considering insulin analogs for managing blood glucose in people with T1D or T2D who frequently experience severe hypoglycemia with human insulin [54]. People who experience frequent episodes of hypoglycemia require periodic SMBG (3 times or more per day) or CGM. Additional suggestions include checking the injection site often (irregular absorption can cause hypoglycemia), adjusting the insulin dose before and after activity, and making sure a CHO supplement and glucometer are readily available [25]. Compared to previously established basal analogs (detemir and glargine U100), ULAA basal analogs (degludec, and glargine U300), have more physiological basal profiles and fewer risks of nocturnal and overall hypoglycemia [10]. It is important to advise people to report to their doctor about episodes of hypoglycemia.

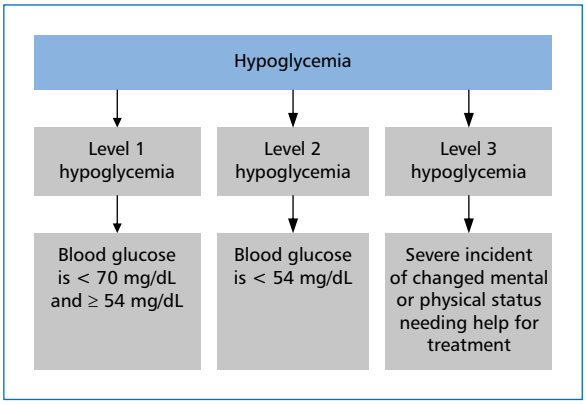

Figure 6. Classification of Hypoglycemia (Adapted from [52])

Management of hypoglycemia

The management of hypoglycemia is summarized in Figure 7. Most episodes of hypoglycemia can be self-treated by ingestion of glucose or CHO-containing juices, soft drinks, candy, other snacks, or a meal. A good amount of CHOs (15–20 g) can be given again in 15–20 minutes if necessary [55]. Since the glycemic response to oral glucose is transient, it is often advised to consume a larger snack or meal soon after the plasma glucose level is corrected to the normal range with oral glucose. When a hypoglycemic person is unable to consume CHOs orally, or in case of severe hypoglycemia, IV glucose or glucagon injection IM or SC is necessary [52].

Fast-acting CHOs should be given to people when their blood glucose falls below the normal range, which is < 70 mg/dL. Although pure glucose ingestion is preferred to correct hypoglycemia, any form of CHO that contains glucose is recommended to raise blood glucose levels rapidly [52].

When someone is unable or unwilling to take glucose or foods orally, hypoglycemia can be treated using glucagon injection IM or SC. Both the person and their caretakers (family members, roommates, school personnel, childcare providers, institution staff, or co-workers, etc.), should be primed about the usage of glucagon which includes glucagon storage and how to give it [52].

For treating hypoglycemia with IV glucose, the use of 5%, 10%, or 25% glucose solutions is preferable over the use of 50% glucose, because, the use of hyperosmolar solutions increases the risk of extravasation damage [56].

In order to reduce hypoglycemia, education on hypoglycemia avoidance, re-evaluation, and treatment regimen adjustments should be made [52]. Precipitating causes need to be investigated at the earliest opportunity and appropriately managed. Education about hypoglycemia prevention and treatment should be part and parcel of every visit of the person by the doctor [55].

Impaired awareness of hypoglycemia

Impaired awareness of hypoglycemia (IAH) is a common side effect of insulin treatment. Around 50% of insulin-treated people with T1D and T2D exhibit hypoglycemia unawareness, and 15–25% have a persistent IAH [57]. Identifying or recognizing a hypoglycemic event by the person is the first step in making HCPs aware of hypoglycemia [58].

Less stringent blood glucose targets, such as a three-month duration without hypoglycemia, as well as instruction on a CSII and CGM, are advised to lower the risk of developing severe hypoglycemia and to try to regain hypoglycemic consciousness [59].

Recommendations

A. Blood glucose < 70 mg/dL is hypoglycemia and any hypoglycemia requiring 3rd party assistance or blood glucose < 54 mg/dL is severe hypoglycemia. **B**

B. Risk or occurrence of hypoglycemia should be assessed at every visit. **C**

C. In a scenario of hypoglycemia or potential hypoglycemia, if there is no access to a glucometer or CGM to check blood glucose levels, the person should be treated based on symptoms and suspicion of hypoglycemia. **B**

D. Oral glucose (15–20 g) or equivalent is to be given for conscious person with blood glucose < 70 mg/dL. If there is continued hypoglycemia (blood glucose < 70 mg/dL) after 15 min, then repeat 15–20 g of oral glucose. Recheck blood glucose after 15–20 mins till the blood glucose is ≥ 70 mg/dL. Once blood glucose ≥ 70 mg/dL, give a snack or meal to prevent further hypoglycemia. **B**

E. Unconscious person with hypoglycemia should be administered IV bolus — 60 mL of 25% dextrose or 150 mL of 10% dextrose or 30 mL of 50% dextrose (only if a lesser concentration is not available due to the risk of extravasation injury) or 1 mg of glucagon IM as soon as possible. **B**

F. After treatment of hypoglycemia in an unconscious person as above with IV dextrose, recheck the blood glucose after 10 mins, and if still < 70 mg/dL, repeat treatment. Once blood glucose ≥ 70 mg/dL, and the person is awake and safe to swallow, allow oral intake of 15–20 g glucose (glucose powder/tablet/honey/sugar/sweet/chocolate). Once blood glucose ≥ 70 mg/dL, and if the person is not safe to swallow, start 5% dextrose IV 100 mL/hr. Repeat BGM every 30 mins and seek help from an expert. **B**

G. Be vigilant for hypoglycemia in people with impaired or declining cognition, advanced age, co-morbidities (renal or hepatic impairments), or decreased food intake due to any reason. **B**

H. Hypoglycemic unawareness is defined as having blood glucose < 70 mg/dL without symptoms. These people should be referred to an expert. **E**

I. Structured patient education about hypoglycemia avoidance, as well as re-evaluation and revision of the treatment plan to reduce hypoglycemia, should be initiated in people with hypoglycemia unawareness or one or more episodes of level 3 hypoglycemia. **B**

J. Insulin-treated individuals with hypoglycemia unawareness, a level 3 hypoglycemic incident, or a pattern of unexplained level 2 hypoglycemia may be encouraged to raise their glycemic goals in order to partially reverse hypoglycemic unawareness and lower the risk of subsequent episodes. **C**

K. Consider insulin analogs over human insulin to manage blood glucose in adults with T1D or T2D who have frequent severe hypoglycemia. **B**

L. Newer ULAA analogs compared with existing basal analogs, have more physiological basal profiles and provide a lower risk of nocturnal hypoglycemia. **B**

M. Short-acting insulin analogs are superior to regular human insulin in reducing hypoglycemia. **B**

N. It is recommended to regularly check the injection sites (irregular absorption can cause hypoglycemia), take the necessary amount of food at mealtimes, adjust the insulin dose appropriately before and after physical activity, and make sure a glucometer and CHO supplements are easily accessible. **A**

O. Periodic SMBG (≥ 3 times a day), or CGM is necessary for people who have frequent episodes of hypoglycemia. **B**

Blood glucose monitoring

Individual glucose monitoring is a valuable tool for the self-management of diabetes, which allows people to evaluate their individual response to therapy and assess whether glycemic targets are being safely achieved. It also provides guidance on dietary changes, physical activity, and medication modification, especially for insulin users. It can help people to improve glucose control, reduce hypoglycemia, and boost self-efficacy [42]. Monitoring blood glucose levels and identifying trends will enable prompt and appropriate modifications to insulin dose, dietary intake, and physical activity management which are the most crucial components of diabetes care. To identify these trends, tools like SMBG using glucometers and CGM can be used [60]. Where glucometers are not available for the individuals due to any reason, at least lab glucose checks are recommended in lieu of glucometer checks.

Self-monitoring of blood glucose

Self-monitoring of blood glucose is the simplest and may be the most useful technique for evaluating the efficacy and safety of glycemic management. SMBG refers to the monitoring and recording of blood glucose levels throughout the day by the person and/or caretaker at home or in a healthcare center [61]. The measured blood glucose levels assist individuals and clinicians in planning proper lifestyle (diet, exercise, and medication) changes.

To ensure that data is used effectively and quickly, both the person with diabetes and the HCPs must examine and analyze data that is recorded using a glucometer. People with diabetes should be educated on how to use BGM data to modify their dietary intake, physical activity levels, or drug therapy to achieve specific goals [61]. Proactive control of diabetes with SMBG can enhance therapeutic results and lower morbidity and mortality [62].

Continuous glucose monitoring

A CGM predicts blood glucose levels by monitoring the concentration of glucose in the interstitial fluid using a sensor implanted directly beneath the skin [63]. Time in range (TIR) is a useful metric of CGM for glycemic control and glucose patterns, and it correlates well with HbA1c [64]. However, people using CGM devices must have access to a glucometer at all times [42]. The guidance on CGM targets for the assessment of glycemic control among various groups is discussed in Table 4.

Table 4. Guidance on CGM Targets for Assessment of Glycemic Control among Various Population Groups (Adapted from [66])

Population groups	Time in range		Time below range		Time above range	
	% of readings; time per day	Target range	% of readings; time per day	Below target level	% of readings; time per day	Above target level
T1D* and T2D	> 70%; > 16 hours, 48 minutes	70–180 mg/dL	< 4%; < 1 hour < 1%; < 15 minutes	< 70 mg/dL < 54 mg/dL	< 25%; < 6 hours < 5%; 1 hour, 12 minutes	> 180 mg/dL > 250 mg/dL
Pregnancy: T1D	> 70%; > 16 hours, 48 minutes	63–140 mg/dL	< 4%; < 1 hour < 1%; < 15 minutes	< 63 mg/dL < 54 mg/dL	< 25%; 6 hours	> 140 mg/dL
Pregnancy: GDM and T2D	Not specified, but > 90% achievable	63–140 mg/dL	Not specified, but < 4% achievable < 1 hour Not specified, but < 1% achievable < 15 minutes	< 63 mg/dL < 54 mg/dL	Not specified, but < 5% achievable 1 hour,12 minutes	> 140 mg/dL
Older/high risk T1D and T2D	> 50%; > 12 hours	70–180 mg/dL	< 1%; < 15 minutes	< 70 mg/dL	< 10%; 2 hours, 24 minutes	> 250 mg/dL

*For age < 25 years, if the HbA1c goal is 7.5%, set time in range target to approximately 60%
GDM — gestational diabetes mellitus; T1D — type 1 diabetes; T2D — type 2 diabetes

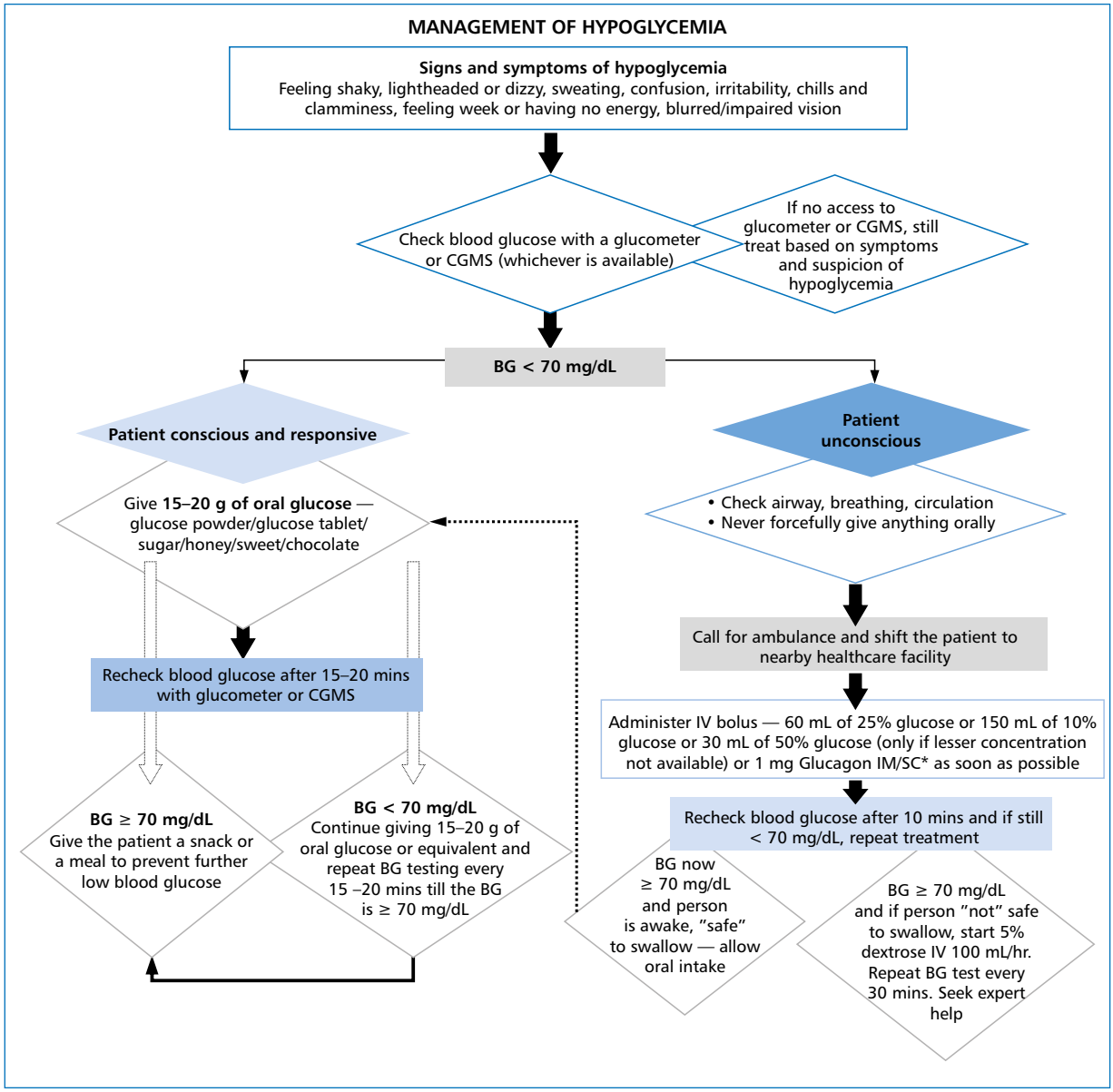

Figure 7. Management of Hypoglycemia (Adapted from [55])
*1 mg IM/SC glucagon injection is a useful alternative to treat hypoglycemia. Monitor for rebound hyperglycemia in T2D after glucagon injection. Review antidiabetic medications and triggers of hypoglycemia
BG — blood glucose; CGM — continuous glucose monitoring; IM — intramuscular; IV — intravenous; SC — subcutaneous; T2D — type 2 diabetes

A. Standardized CGM metrics

The worldwide agreement on TIR offers recommendations for common CGM measurements (Fig. 8) and things to keep in mind when using them in clinical interpretation and treatment [65]. Time above range (TAR) and time below range (TBR) are additional helpful metrics for adjusting insulin doses and re-evaluating the treatment strategy. According to the most recent advanced technologies and treatments for diabetes (ATTD) international TIR consensus 2019, most people with T2D should aim to spend > 70% of their time per day (approx. > 17 h) in TIR (70–180 mg/dL), < 4% in TBR (< 70 mg/dL) and < 25% of the time per day in TAR (> 180 mg/dL) [66].

BGM and CGM can help manage medications, guide medical nutrition treatment, encourage physical activity, and prevent hypoglycemia [42]. The CGM measures TIR (including TAR and TBR) and gives insights for a more individualized diabetes treatment plan [64]. These indicators are now being incorporated into clinical practice.

In those who can afford, the use of CGM devices should be considered as soon as diabetes is diagnosed and insulin therapy is initiated [67]. This relieves the

1	Number of days CGM device is worn (recommend 14 days)	
2	Percentage of time CGM device is active (recommend 70% of data from 14 days)	
3	Mean glucose	
4	Glucose management indicator	
5	Glycemic variability (% CV) target ≤ 36%*	
6	TAR: % of readings and time > 250 mg/dL	Level 2 hyperglycemia
7	TAR: % of readings and time 181–250 mg/dL	Level 1 hyperglycemia
8	TAR: % of readings and time 70–180 mg/dL	In range
9	TBR: % of readings and time 54–69 mg/dL	Level 1 hypoglycemia
10	TBR: % of readings and time < 54 mg/dL	Level 2 hypoglycemia

Figure 8. Standardized CGM Metrics (Adapted from [65])
*Some studies suggest that lower %CV targets (< 33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas.
CGM — continuous glucose monitoring; CV — coefficient of variation; TAR — time above range; TBR — time below range; TIR — time in range

strain of regular BGM and enables close monitoring of glucose levels with adjustments to insulin dose and lifestyle changes.

B. Types of CGM

CGMs are classified into two types based on data type: "real-time" and "flash." Real-time CGMs (rtCGM) send glucose readings every 1–5 minutes over Bluetooth to a chosen receiver, mobile, or insulin pump. Flash CGMs, also known as intermittently scanned CGMs (isCGM) record glucose concentrations every 1–15 minutes, but downloads the data only to the designated reader when the user "flashes" the near field communication tag, at a point where the past 8 hours of data is retrieved [63].

Professional CGMs are CGM devices that are attached to a person with diabetes at the doctor's clinic under remote control and worn for a specific amount of time (generally 7–14 days). The data is utilized to evaluate glycemic trends and patterns. Unlike rtCGM and isCGM devices, these are clinic-based and are not owned by the people [42].

Recommendations

A. BGM using a glucometer or CGM is an essential part of the insulin care plan. **B**

B. People with diabetes should be encouraged to use BGM devices as indicated by their circumstances, preferences, and treatment. **B**

C. Individuals who are on insulin using BGM should be encouraged to check blood glucose reading when appropriate as suggested by the physician and based on their insulin regimen. **B**

D. It is essential to individualize the type and selection of devices based on a person's specific needs, desires, skill level, and device availability. **A**

E. When it comes to an individual whose diabetes is partially or totally managed by someone else (such as a person with cognitive disability), the talents and preferences of the carer are critical to the decision-making process. **A**

F. When recommending a device, ensure that those with diabetes and their carers receive initial and ongoing instructions and training, either in-person or online, as well as regular evaluations of the technique, outcomes, and their capacity to use data, including uploading/sharing data (if applicable), to adjust therapy. **B**

G. Initiation of CGM, CSII, and/or automated delivery of insulin might be advantageous depending on a person's/caregiver's requirements and preferences and should be referred to an Endocrinologist or a physician with such skills. **B**

H. Glucometers are important tools to monitor capillary glucose in the comfort of one's own home and are to be considered wherever appropriate. **A**

I. Regular SMBG is strongly recommended for people who are on BBR insulin therapy, on pregestational/gestational diabetes mellitus (GDM) using insulin, history of hypoglycemia unawareness, brittle diabetes, or with poor metabolic control on multiple OADs and/or insulin. **A**

J. Glucometer readings should not be used to diagnose T2D. **B**

K. Basal insulin is best monitored by FPG and should be monitored at least once a week. During initiation and intensification, more frequent monitoring is required. **A**

L. Prandial insulin is best monitored by paired premeal and post-meal glucose values. **B**

M. Premix insulin is monitored by fasting and premeal glucose values. **B**

N. CGM is a valuable tool in deriving information pertaining to glucose control, glucose variations, hypoglycemia, and the trends of the same. **B**

O. CGM targets for most adults with T2D and T1D aim to spend > 70% of their time per day (approx. > 17 h) in TIR (70–180 mg/dL), < 4% in TBR (< 70 mg/dL) and < 25% of the time per day in TAR (> 180 mg/dL). **E**

P. People using CGM devices must have access to glucometer at all times. **A**

Insulin pump

CSII commonly known as insulin pumps are devices that deliver RAA throughout the day in order to regulate blood glucose levels. A CSII or insulin pump attempts to replicate pancreatic activity [68].

Factors to take into account when starting pump therapy in people with diabetes include affordability, assessment of the person's and their family's readiness, selection of the pump type and initial pump settings, individual/family education on potential pump complications, transition from BBR, and introduction of advanced pump settings [42].

Insulin pumps are safe and efficient in young people with T1D to achieve their desired glycemic results while lowering their risk of hypoglycemia and DKA, enhancing their QoL, and avoiding long-term consequences [42].

CSII, an alternative to BBR, has been linked to better long-term results in intensive insulin treatment for T2D glycemic control [69]. Adults with severe hypoglycemia were less likely to experience severe episodes while receiving CSII through pump treatment.

Recommendations

A. Insulin pump therapy may be recommended to people with T1D, people with GDM, those with T1D or T2D whilst pregnant, people with T2D who fail to achieve acceptable glycemic control with a basal/bolus regimen, those who have remarkably high insulin requirements, severe insulin resistance syndromes such as lipodystrophy, and people with insulin insufficiency (those who have undergone a pancreatectomy and/or those with cystic fibrosis). **B**

B. Structured education, CHO counting and training should be provided regarding insulin pump use, including aspects such as infusion set insertion technique and basic insulin dose adjustments at the initiation of the insulin pump therapy. **A**

Intravenous insulin infusion

Intravenous insulin infusion is useful in people who are critically ill, in hyperglycemic emergencies, those with uncontrolled hyperglycemia on SC insulin regimens, and during the perioperative phase, people with NBM status or during labor [17]. There are no absolute contraindications to using IV insulin infusion, and the important precaution to take is to avoid hypoglycemia. Hypokalemia is a potential problem during usage of IV insulin; hence serum potassium levels need to be monitored and replaced appropriately. IV insulin has a rapid onset of action and a very short half-life, allowing its dose to be easily titrated in response to changing blood glucose levels [17].

In hospitalized people, insulin is the quickest and most effective medication for attaining glycemic control.

Indications of IV insulin

- Uncontrolled hyperglycemia despite the use of multiple SC insulin injections
- DKA or HHS
- During childbirth and before an emergency surgery
- People who are extremely ill, such as those with sepsis and septic shock
- People with NBM status, or who have inconsistent meal patterns in terms of timing or nature
- Perioperative period
- Organ transplantation
- High-dose glucocorticoid treatment
- Dose-finding strategy prior to conversion to SC insulin

The majority of hospitalized people, with and without serious illnesses should maintain a blood glucose target of 140–180 mg/dL. In cases where a lower target of 110–140 mg/dL may be achieved without causing significant hypoglycemia, such tight glucose targets may be considered [70]. On the other hand, for terminally ill people, people with significant comorbidities, and people in situations where frequent BGM is not practical or if one is concerned about hypoglycemia, one may accept a target of < 250 mg/dL [70]. Less severe insulin regimens are more suitable in these people to reduce glucosuria, dehydration, and electrolyte abnormalities. The use of a sliding scale SC insulin regimen is strongly discouraged in the inpatient hospital setting [70].

Ideally, BBR is the treatment of choice in non-ICU hospital settings. For the majority of noncritically ill hospitalized people who receive appropriate nourishment, an insulin regimen including basal, prandial, and correction components is the optimal course of treatment. Usually, all OADs have to be stopped and insulin is initiated at a very low threshold in hospitalized people. Few selective DPP4i may be continued where appropriate considering other comorbidities [70].

Transition from intravenous to subcutaneous insulin

A transition procedure is advised when stopping IV insulin since it is linked to decreased morbidity [70]. It may be appropriate to consider administering a person with T1D or T2D, a dose of SC basal insulin 2 hours before transitioning from an IV infusion to an SC regimen due to the short half-life of IV insulin and the delayed onset of action of SC basal insulin. Initiating SC basal insulin before stopping an IV insulin may help reduce hyperglycemia [71]. The insulin dosage is best determined based on the insulin infusion rate during the last 6 hours when stable glycemic objectives were met [72]. Usually, the last 6 hours' IV insulin administered is multiplied by 4 to get the total SC insulin that is required over 24 hours. Of the total calculated daily SC insulin requirement, 40% is given as basal SC injection, and the rest 60% is divided into three doses of bolus SC insulin injections over a span of 24 hours. Whilst calculating this, other factors such as the IV fluids that were being administered such as IV dextrose, any inotropes, or corticosteroids that were being administered, need to be taken into consideration. There needs to be an overlap of 30 minutes of IV insulin, after SC bolus insulin is given while transitioning from IV to SC insulins [17].

Hypoglycemia is a crucial consequence that has to be minimized during hospitalization due to dysregulated metabolism and/or diabetes treatment. Each hospital should thus establish and put into practice a hypoglycemia prevention and management plan. If a person's blood glucose level is < 70 mg/dL, a standardized hospital-wide, hypoglycemia treatment strategy ought to be in place [73]. Additionally, every person should have their unique strategy created for both avoiding and managing hypoglycemia [74].

Recommendations

A. Insulin is the suggested treatment modality in hospitalized people. Few OADs such as selective DPP4i can be used safely in certain scenarios. **A**

B. HbA1c test should be done in all people with diabetes/or hyperglycemia (blood glucose > 140 mg/dL) admitted to the hospital if not done in the past 3 months. **B**

C. Insulin administration should be based on validated protocols that allow for adjustments of insulin dosage based on glycemic fluctuations. **B**

D. Target glucose range for the majority of critically ill and non-critically ill people is 140–180 mg/dL and a more stringent goal of 110–140 mg/dL can be targeted for selected individuals if this can be achieved without hypoglycemia. **A**

E. Ideally, BBR is the treatment of choice in non-ICU hospital settings. **A**

F. The preferred treatment for non-critically ill hospitalized people with poor nutritional intake is basal insulin or a basal plus bolus correction insulin regimen. **B**

G. For the majority of non-critically sick hospitalized persons who get adequate nourishment, an insulin regimen including basal, prandial, and correction components is the optimal course of therapy. **B**

H. Use of sliding scale SC insulin regimen is strongly discouraged in the inpatient hospital setting. **A**

I. In a critical care environment, and ideally, in individuals who are NBM, continuous IV insulin infusion is the best way to meet glycemic goals. **B**

J. It should be ensured that there is continuity between IV insulin infusion and the first dose of SC insulin. There needs to be an overlap of 30 minutes while transitioning from IV to SC bolus insulins. **B**

K. Once competency is demonstrated and appropriate supervision is available, people with diabetes who are capable of utilizing diabetes equipment, such as insulin pumps and CGM systems safely should be encouraged to do so while receiving inpatient care or during outpatient treatments. **A**

L. While transitioning from the hospital to the ambulatory setting, a detailed discharge plan should be tailored to the individual with diabetes. **B**

Insulin therapy in special populations

Pregnancy

A. Pregnancy planning and preconception

All women of reproductive age with diabetes should be advised about the necessity of reaching and maintaining euglycemia as safely as possible prior to conception and throughout pregnancy. Family planning should be discussed, and effective contraception advice should be provided until a woman's treatment regimen and HbA1c are optimal for pregnancy. Preconception counselling should emphasize the significance of obtaining glucose levels as near normal levels as safely achievable, preferably HbA1c < 6.5%, to lower the risk of congenital abnormalities, preeclampsia, macrosomia, premature birth, and other problems [74].

Prior to pregnancy, all drugs that are risky in pregnancy should be discontinued, including OADs [74]. When corticosteroids are used in pregnancy for fetal lung maturation or any other indication, BGM and proactive optimization of glycemic control using insulin are mandatory [75]. Insulin is the drug of choice for treating hyperglycemia in pregnancy [3, 74]. Metformin can be used in certain circumstances where clinically appropriate [3].

While GDM is the primary cause of hyperglycemia found in pregnancy, preexisting T1D and T2D account for most of the remaining [25]. Glucose targets for pregnant women with diabetes are FPG < 95 mg/dL, 1-hour PPG < 140 mg/dL, and 2-hour PPG < 120 mg/dL, whilst avoiding hypoglycemia. HbA1c should be used as a supplementary indicator of glycemic control during pregnancy [74]. CGM when used in conjunction with pre and postprandial BGM, aids in the achievement of glycemic control in GDM [74].

B. Gestational diabetes mellitus

It is recommended to initiate insulin along with lifestyle changes if nutrition treatment or a meal plan fails to help women with GDM achieve their blood glucose goals, usually within two weeks of starting them [76]. As insulin does not cross the placenta significantly, it is the preferred medication for treating hyperglycemia in GDM. When compared to regular in-person treatment alone, telehealth consultations in addition, for pregnant women with GDM may enhance outcomes [74]. Both insulin aspart and insulin lispro have been demonstrated to be safe and effective for usage during pregnancy [77]. BBR or insulin pump technologies can be used for T1D-complicated pregnancy. BBR is the regimen of choice; however, a premix regimen can be considered in a resource-constrained setting. Information on available insulin analogs and associated pregnancy categories are summarized in Table 5.

C. Pre-existing T1D or T2D

Insulin is the drug of choice for people with preexisting T1D and T2D in pregnancy as it does not cross the placenta, in significant quantity. Structured education about the prevention, detection, and treatment of hypoglycemia is vital before, during, and after pregnancy, in people with diabetes and their family members [74]. In a meta-analysis of three available RAA (insulin lispro, aspart, and glulisine, respectively) in pregnant women with T1D or GDM, insulin lispro, and insulin aspart were found to be safe and effective for both mother and fetus, with glycemic control at least as good as with regular human insulin [78]. Women with diabetes planning pregnancy or who have become pregnant should be counselled on the risk of development and/or progression of diabetic retinopathy [74].

D. Blood glucose monitoring during pregnancy

Frequent SMBG is necessary to guide the treatment of GDM. To achieve ideal glycemic targets, ADA recommends performing SMBG four times daily, (one fasting and 3 tests post breakfast, post lunch, and post dinner) in both GDM and pre-existing T1D and T2D. However, individuals with pre-existing T1D or T2D should monitor their blood glucose levels pre-prandial also, i.e., seven tests each day, (one fasting, three before and three after each meal) [74].

CGM, when used in conjunction with pre and post-meal BGM, can aid in achieving the glucose targets in pregnant women with diabetes. rtCGM when used in addition to BGM, helps to lessen macrosomia and newborn hypoglycemia in pregnancies complicated by T1D. It is not recommended to utilize standard estimates of HbA1c or glucose control indicator calculations during pregnancy [74].

E. Postpartum care

Insulin resistance decreases significantly, immediately after childbirth. Hence, insulin requirements must be monitored carefully and insulin doses should be reduced in those with pre-existing DM or even stopped in those with GDM [74].

F. Lactation

For mothers with prior GDM, breastfeeding lowers their chance of acquiring T2D [74]. A change in insulin dosage may be necessary since nursing might cause nocturnal hypoglycemia.

Breastfeeding women should be encouraged to follow an individualized diet. It is important to ensure that women with diabetes previously treated with insulin, understand that they are more likely to have hypoglycemia in the postpartum period, particularly if they are breastfeeding, and encourage them to have a snack between meals.

Table 5. Table of Available Insulin Analogs and Associated Pregnancy Category (Adapted from [79])

Type of insulin	Time to onset	Peak time	Duration	Does it cross the placenta?	Pregnancy category
Aspart	10–15 min	40–50 min	3–5 hours	Unlikely at therapeutic concentrations	B
Lispro U100 and U200	10–15 min	30–90 min	3–5 hours	Yes, at single doses > 50 units	B
Glulisine	10–15 min	55 min	3–5 hours	Unknown	C
Detemir	1–2 hours	None	24 hours	Unknown	B
Glargine U100	1–2 hours	None	24 hours	Unlikely at therapeutic concentrations	No human pregnancy data (previously C)
Glargine U300	> 6 hours	None	24 hours	Unlikely at therapeutic concentrations	No human pregnancy data
Degludec U100 and U200	1 hour	None	42 hours (at steady state)	Unknown	C

FDA Pregnancy Categories (Mentioned Above)

A Controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters). The possibility of fetal harm appears remote.

B Animal reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in women, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
OR
Animal studies have shown an adverse effect that was not confirmed in controlled studies in women.

C Animal reproduction studies have shown an adverse effect on the fetus, there are no controlled studies in women, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
OR
Animal studies have not been conducted, and there are no controlled studies on women.

D There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in women, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

X Studies in animals or women have demonstrated fetal abnormalities.
OR
There is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit.

Recommendations

A. Preconception counselling should be incorporated into routine diabetes care for all women with T2D in the reproductive age group. **A**

B. Effective reversible contraception is recommended until the treatment regimen and HbA1c are optimized for pregnancy. **A**

C. Preconception counselling should cover the significance of establishing glucose levels as close to normal as possible, preferably HbA1c < 6.5% to lower the risk of congenital abnormalities, preeclampsia, macrosomia, premature birth, and other problems. **A**

D. Once a woman with diabetes decides to plan pregnancy in the near future, medications need to be optimized. **A**

E. All oral medications used for glucose control other than metformin need to be stopped while planning pregnancy. **B**

F. Insulin is safe in pregnancy and may be started if required for optimal glucose control. **A**

G. Statins, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) need to be stopped. **B**

H. Women with diabetes planning pregnancy or who have become pregnant should be counselled on

the risk of development and/or progression of diabetic retinopathy. **B**

I. Glucose targets for pregnant women with diabetes are FPG < 95 mg/dL, 1-hour PPG < 140 mg/dL, and 2-hour PPG < 120 mg/dL, whilst avoiding hypoglycemia. **B**

J. HbA1c is slightly lower in pregnancy; the ideal target in pregnancy is < 6% if it can be achieved without significant hypoglycemia. The target may be relaxed to < 7% in certain cases to prevent hypoglycemia. **B**

K. HbA1c targets in diabetes and pregnancy can be facilitated by CGM. **B**

L. Insulin is the drug of choice for treating hyperglycemia in GDM. Metformin can be used in certain circumstances where clinically appropriate. **A**

M. All insulins can be used in pregnancy. However, class B insulins are preferred over class C, class D. **C**

N. Regular insulin or RAA may be used in women with preexisting diabetes to improve PPG. **B**

O. BBR is the regimen of choice. However, premix can be considered in resource-constrained settings. **B**

P. In a pregnancy complicated by T1D, either BBR or insulin pump technology can be recommended. **A**

Q. When corticosteroids are used in pregnancy for fetal lung maturation or any other indication, BGM and proactive optimization of glycemic control using insulin is mandatory. **E**

R. In women with diabetes poorly controlled on BBR, consider initiation of CSII, ideally at preconception. **A**

S. An ideal SMBG would be seven tests each day, one fasting, three before and three after each meal. If this is not possible, encourage one fasting test, and three tests, that are performed daily two hours after breakfast, lunch, and dinner. **C**

T. Insulin resistance lowers significantly immediately following delivery, and insulin requirements must be monitored and reduced or stopped as appropriate in the postpartum period. **C**

U. Educate women with insulin-treated pre-existing diabetes about their higher risk of hypoglycemia in the postpartum period, particularly while breastfeeding, and advise them to have a snack between meals. **B**

Elderly

Diabetes is a highly heterogeneous condition and a major health concern among the elderly. Regular evaluations of the medical, psychological, functional, and social domains are necessary for managing diabetes in older persons [80]. When evaluating older persons who have diabetes, it is crucial to correctly classify the type of diabetes, as well as other elements including its duration, the presence of complications, other comorbidities, and treatment-related concerns like hypoglycemia and anxiety. Screening for diabetes complications in older persons should be tailored to each individual and repeated regularly as the findings of screening tests may influence targets and treatment methods [80].

Episodes of hypoglycemia should be identified and treated during every visit. Older persons are more likely to have hypoglycemia for a variety of reasons, including insulin deficiency, which necessitates insulin treatment, and growing renal insufficiency. CGM is advised for older people with T1D and T2D to lessen hypoglycemia and to enhance glycemic outcomes and reduce glucose variability [80].

A. Glycemic targets in elderly people

Elderly adults with no coexisting chronic illnesses as well as unimpaired cognitive function and a good functional status may aim for stringent glycemic goals (HbA1c < 7.0–7.5%) if achievable without hypoglycemia. Older adults with multiple coexisting chronic illnesses, cognitive impairment, or functional dependence should have less stringent goals (HbA1c < 8.0%). Glycemic targets may be reduced for the elderly as part of individualized therapy [80].

It is important to avoid overtreating elderly persons with diabetes. It is advised that complex treatment regimens (particularly insulin) are simplified to lower the risk of hypoglycemia and for convenience. Polypharmacy needs to be avoided, wherever feasible, to reduce pill burden, drug interactions, and cost [80].

The usage of pens over syringes and analog insulins over human insulin needs to be considered for safety, flexibility, and convenience in the geriatric population. Telemedicine consultations offer convenience and continuity of care for diabetes, especially for the elderly, similar to pregnancy. Costs of care need to be considered when designing treatment plans, to limit cost-related obstacles to adherence [80].

Recommendations

A. For older adults on insulin, CGM can be recommended where appropriate. **A**

B. Elderly adults with no coexisting chronic illnesses as well as unimpaired cognitive function and a good functional status may aim for stringent glycemic goals (HbA1c < 7.0–7.5%) if achievable without hypoglycemia. **C**

C. Older adults with multiple coexisting chronic illnesses, cognitive impairment, or functional dependence should have less stringent goals (HbA1c < 8.0%). **B**

D. Simplification of complex regimens is recommended to lower the risk of hypoglycemia, for safety, flexibility, and convenience. **B**

E. Usage of pens over syringes and analog insulins over human insulin needs to be considered for safety, flexibility, and convenience in the geriatric population. **B**

F. Telemedicine consultations offer convenience and continuity of care for diabetes, especially for the elderly as in pregnancy. **A**

G. Older adults with diabetes on insulin have a greater risk of hypoglycemia hence episodes of hypoglycemia should be ascertained and addressed at every visit. **B**

Insulin therapy during fasting

Many people with diabetes fast for religious reasons, increasing the risk of severe hypoglycemia. Insulin resistance/deficiency during fasting might result in excessive glycogen breakdown and increased gluconeogenesis [81]. When using insulin therapy during religious fasting, the person must be informed about the hazards associated with fasting, made familiar with SMBG, follow the recommended diet, engage in safe exercise, and modify their insulin doses accordingly [82]. People with T2D on intensive insulin therapy should be advised to refrain from fasting.

Individuals with a history of DKA, recurrent hypoglycemia, hypoglycemic unawareness, people on complex insulin regimes, people with end-organ damage, individuals with suboptimal glycemic control, pregnant and lactating women, people with T1D, and elderly individuals should be discouraged from fasting [82]. Individualized physician recommendations for changing the dose and timing of insulin injections during the fasting interval should be followed.

During fasting, frequent SMBG or CGM is indicated to reduce the risk of hypoglycemia and detect episodes of hyperglycemia. Planning meals with low glycemic index CHOs that include fruits, vegetables, and lean meats is necessary during fasting days. Sweets, sweetened beverages, and fried meals should be avoided [83].

CHO counting during meals assists in optimizing the dosage of insulin administration. During non-fasting hours, it is recommended to stay hydrated by sipping water and other non-sweetened beverages frequently. If hypoglycemia develops, the person should be advised to break the fast immediately, irrespective of the time [83]. Structured patient education about BGM, nutritional advice, exercise advice, medication dosage and timing, adjustments, symptoms of complications, and how to treat them is recommended [83].

Recommendations

A. People with T2D who are on intense insulin treatment should avoid fasting. **B**

B. More frequent BGM is recommended while fasting to reduce the risk of hypoglycemia and detect episodes of hyperglycemia. **B**

C. Individuals with a history of DKA, recurrent hypoglycemia, hypoglycemic unawareness, people on complex insulin regimes, people with end-organ damage, people with suboptimal glycemic control, pregnant and lactating women, people with T1D, and elderly individuals should be discouraged from fasting. **A**

D. Structured and individualized patient education about BGM, nutritional advice, exercise advice, medication dosage and timing, adjustments, symptoms of complications, and how to treat them is recommended. It should also include when to break a fast in order to minimize complications. **E**

Sick day management

Sickness is frequently associated with elevated blood glucose levels and an increased risk of ketoacidosis in those with T1D and others with DM who are insulin-dependent [49]. Insulin requirement increases significantly during acute sickness which eventually requires increased frequency of BGM. Depending on their glucose levels, people may require RAA, every 2 to 4 hours [25]. Additionally, ketone testing during sickness may aid in the management of individuals suffering from acute vomiting or hyperglycemia. It is critical to recognize the early signs and symptoms of DKA to prevent it [25]. Individuals and/or carers who suspect it should contact their doctor as soon as possible.

During an illness, the following are important to remember in those with T1D and others with DM who are insulin dependent. Check blood glucose levels periodically at least every four hours or more frequently if necessary. If blood glucose levels are consistently high (> 250 mg/dL) or if the person has vomiting, stomach discomfort, or rapid breathing, it is recommended to check for blood or urine ketones [49]. The person should be sent to the hospital right away if they have high ketones (> 17.43 mg/dL)/diarrhea more than three times in 24 hours or a temperature above 101°C for 24 hours [49].

In case of low blood glucose levels, a small dosage of glucagon or consuming CHOs and/or juices regularly is recommended. To maintain adequate calorie intake, drinking more calorie-free liquids, semi-solid meals, and beverages, such as thin soups, milk, buttermilk, or fresh lime juice, should be encouraged [49]. However, individuals should be encouraged to eat normally if they can tolerate it. Insulin doses may be lowered but should not be skipped entirely. Never stop insulin completely, especially basal insulin, as this is a typical error. If in doubt about managing during sick days, it is recommended to seek an expert opinion immediately [49].

Recommendations

A. In people with insulin-dependent diabetes, during sick days, it is recommended to continue taking insulin with dose adjustments. **B**

B. Individuals need to be advised to check their blood glucose and ketone levels at least every four hours and to keep track of the findings. **B**

C. Drinking more calorie-free liquid is recommended. However, persons should strive to eat normally if tolerated. **C**

D. Low blood glucose can be treated with a small dosage of glucagon or by consuming CHOs and/or juices on a regular basis. **C**

E. Although insulin dosages can be decreased, complete stoppage of insulin is dangerous, especially basal insulin. **B**

F. Maintaining an adequate calorie intake, semi-solid meals, and beverages, such as thin soups, milk, buttermilk, or fresh lime juice, should be encouraged. **B**

G. To control the elevated blood glucose levels, the insulin dosage may need to be raised, and extra doses of fast-acting insulin may be required. **B**

H. If blood glucose remains consistently high (> 250 mg/dL), it is important to check blood or urine ketones in all insulin-dependent patients with diabetes during sick day periods. **B**

I. The person should be sent to the hospital right away if they have high ketones (> 17.43 mg/dL)/diarrhea more than three times in 24 hours or a temperature above 101°C for 24 hours or clinically unwell. **A**

Safety precautions for insulin users who drive

Disclaimer: It is strongly advised that individuals with diabetes should strictly adhere to the law of the land and follow their clinician's advice. These recommendations here are only a guide made based on the best available clinical evidence and consensus of the Association of Clinical Endocrinologists group.

The ability to drive safely in people with diabetes may be hampered by its symptoms or consequences, which can affect driving fitness in a variety of ways, including but not limited to hypoglycemia, hyperglycemia, vision impairment, peripheral neuropathy, and other diabetes problems. Furthermore, driving necessitates a high metabolic demand, which may lead to hypoglycemia episodes in individuals with diabetes which might result in driving errors and road traffic accidents [84]. Hence, precautions ought to be taken to protect themselves, co-passengers, and other road users.

People with diabetes should be advised to always have their glucometer, blood glucose strips, or CGM with them. It is recommended to check their blood glucose levels before the trip and for every two hours after they start driving. Frequent testing may be essential if there is a higher risk of hypoglycemia for any reason, such as after physical exercise or a change in meal schedule. If the blood glucose values are ≤ 90 mg/dL, it is recommended to advise them to have a snack. "Never drive if blood glucose is in the hypoglycemic range or if the person feels hypoglycemic" should be the dictum [85].

It is recommended to always maintain an emergency supply of fast-acting CHOs, such as glucose, or sweets, or chocolates, in the vehicle. The person needs to be advised to consume regular meals and snacks and take breaks during long journeys. It is recommended to always avoid alcohol while driving [85].

Recommendations

A. Disclaimer: It is strongly advised that individuals with diabetes should strictly adhere to the law of the land and follow their clinician's advice. **A**

B. Hypoglycemia in individuals who are on insulin medication or other antidiabetic therapy is detrimental. Hence, precautions should be taken to protect themselves, co-passengers, and other road users. **A**

C. People with diabetes should be advised to always have their glucometer, blood glucose strips, or CGM with them. **B**

D. Individuals need to be advised to check their blood glucose before the trip and for every two hours after they start driving. **B**

E. There should be a maximum of 2 hours between the pre-driving glucose check and the first glucose check after driving has begun. **B**

F. If there is a higher risk of hypoglycemia for any reason, such as after physical exercise or a change in meal schedule, more frequent testing may be necessary. **C**

G. If the blood glucose values are ≤ 90 mg/dL, it is recommended to advise them to have a snack. Never drive if blood glucose is in the hypoglycemic range or if the person feels hypoglycemic. **B**

H. It is recommended to always maintain an emergency supply of fast-acting CHOs, such as glucose or sweets, or chocolates in the vehicle. **B**

I. Individuals need to be advised to consume regular meals and snacks and take breaks on long journeys. Always avoid alcohol while driving. **A**

J. If a person suffers a hypoglycemic attack while driving, they should not start driving until 45 minutes after their glucose level has recovered to normal (at least 90 mg/dL) and also feeling absolutely normal. **B**

Alcohol and insulins

People with diabetes who consume alcohol should be advised to avoid or limit alcohol intake [55]. Alcohol intake is associated with risks such as weight gain, hyperglycemia (for those who consume excessive quantities of CHO-rich drinks), and hypoglycemia (especially for those taking insulin or insulin secretagogue therapy) [86].

Individuals with diabetes should be educated about the indications, symptoms, and self-management of delayed hypoglycemia after drinking alcohol, especially spirits, and if they are on insulin or insulin secretagogues [87]. It is also important to emphasize the need of glucose monitoring after consuming alcoholic drinks in order to limit the risk of hypoglycemia [86].

Recommendations

A. People with diabetes who drink alcohol should be advised to avoid or limit alcohol intake and those who smoke should be advised smoking cessation and not to use any tobacco products. **C**

B. It is recommended that all individuals with diabetes who are on insulin should have healthy snacks before consuming any alcohol drinks that are high in alcohol percentage, to avoid hypoglycemia. **B**

C. Certain alcohol beverages rich in CHOs, such as sweet cocktails may cause spike in blood glucose which warrants insulin dose adjustments with appropriate BGM. **C**

Others

A. Hepatic impairment

People with both diabetes and hepatic impairment are more likely to be seen in clinical practice as they are at risk of developing non-alcoholic fatty liver disease (NAFLD). NAFLD and T2D frequently coexist, raising the risk of dangerous hepatic and extra-hepatic effects.

Individuals with hepatic impairment who need insulin treatment should select regimens with a reduced risk of hypoglycemia. Insulin analogs should be considered in people with T2D and hepatic impairment for enhanced glycemic control with minimal risk of hypoglycemia [25].

B. Chronic kidney disease

People with diabetes and chronic kidney disease (CKD) have a biphasic pattern in their insulin needs. In the early stages, more insulin is required to establish glycemic control due to insulin resistance, but as advanced renal failure progresses and creatinine clearance falls < 50 mL/min, insulin need decreases or, in extreme cases, insulin may have to be even stopped [88].

CKD risk and progression can be reduced by optimizing blood glucose and regulating blood pressure. All insulins are regarded as safe across the CKD spectrum [25]. However, ultralong and ultrashort-acting insulins are preferred for safety, flexibility, and convenience. Nevertheless, with decreasing estimated glomerular filtration rate (eGFR) readings, insulin dosages in CKD might have to be decreased [89]. Among basal insulins, detemir and glargine appear to be safe and effective and among prandial insulins, both regular insulin and RAA appear to be safe and efficacious [25].

In CKD people with glomerular filtration rate (GFR) between 15–60 mL/min and < 15 mL/min, prompt adjustments with a reduction to 75% and 50% in insulin TDD respectively are often necessary. However, in people with GFR > 60 mL/min, no dose modifications may be needed [25].

People on dialysis are at an increased risk considering glucose fluctuations. It may be required to lower the basal insulin dosage by up to 25% on days of hemodialysis (HD) to avoid hypoglycemia [90]. People undergoing HD are usually advised to avoid short-acting insulins during and immediately before HD [91].

During peritoneal dialysis (PD), insulin may be administered SC, or along with the dialysis fluid. If insulin is administered along with dialysate, an increase of up to 30% may be necessary to minimize the effects of dextrose absorption for the PD fluids and for the loss of tubing and dilution [90]. Hence, the lowest possible dialysate dextrose concentration should be used as a PD fluid as much as possible [92].

Overall, a lacune exists in the literature concerning recommendations for adjusting insulin therapy when initiating HD or PD, or when switching between the two.

C. Cardiovascular disease

The link between insulin and cardiovascular disease (CVD) is complicated. People with diabetes are more likely to develop CVD and its related clinical consequences. Premix insulins are more successful in lowering PPG than basal insulin analogs [15]. The insulin regimen selected should be individualized and based on the severity of hyperglycemia, the risk of hypoglycemia, and the possibility of interventional operations in the near future. If the glycemic objective is not met after adding basal insulin, a basal plus/premix regimen should be explored before moving on to a BBR [25].

People with T2D who are receiving combination treatment with premix insulin analogs and OADs should be closely evaluated for signs and symptoms of heart failure (HF), weight gain, and edema, and quick clinical intervention is advised if cardiac symptoms worsen [15]. Wherever appropriate, concomitant SGLT2i and/or GLP-1RA use along with insulins helps reduce the TDD of insulin, lessen weight gain and hypoglycemic episodes.

D. Post-transplantation diabetes mellitus (PTDM)

An acceptable step-by-step method for the management of late PTDM is lifestyle change followed by OADs and insulin. People with acute post-transplant hyperglycemia, however, should be managed in the opposite order from how it appears above [25]. Insulin is the drug of choice for the management of hyperglycemia, PTDM [10]. During the initial few months following transplantation, insulin treatment should be favored [25].

E. Post-immunotherapy new-onset diabetes (PINOD)

In general, less than 1% of individuals who receive immunotherapy develop new-onset DM [25]. Insulin is recommended as the preferred treatment for these individuals [25].

F. Glucocorticoid-induced hyperglycemia (GIH)

GIH and glucocorticoid-induced diabetes are linked to higher rates of mortality and morbidity and may have exacerbated long-term microvascular and macrovascular risks. The co-existence of inflammatory disorders and GIH further increases the risk of CVD. The coronavirus disease 2019 (COVID-19) pandemic has increased the clinical importance of glucocorticoid treatment by increasing the number of hospital admissions for acute viral infection. It has been demonstrated that COVID-19 increases the incidence of hyperglycemia and is linked to greater incidences of DKA, HHS, and new-onset diabetes. All patients undergoing high-dose glucocorticoid medication should have BGM for at least 48 hours after cessation of glucocorticoid treatment, and SC insulin therapy should be initiated as needed. The type of glucocorticoid and duration of action must be considered in determining insulin treatment regimens. For individuals who are on higher doses of glucocorticoids, an increase in the dosage of prandial and correctional insulin may be needed in addition to basal insulin [93]. The dose of correctional insulin is based on the dose of the administered glucocorticoid and the weight of the person [94].

Recommendations

A. Insulin analogs should be considered in people with T2D and hepatic impairment for enhanced glycemic control with minimal risk of hypoglycemia. **E**

B. All insulins are considered safe across the spectrum of CKD. However, ultralong and ultrashort-acting insulins are preferred for safety, flexibility, and convenience. **B**

C. It is recommended to consider lowering the basal insulin dosage by up to 25% on days of HD to avoid hypoglycemia. **B**

D. Individuals undergoing HD are usually advised to avoid short-acting insulins during and immediately before HD. **B**

E. In people undergoing PD, an increase of insulin dose up to 30% may be necessary to minimize the effects of dextrose absorption for the PD fluid. If possible, non-dextrose fluids to be used in lieu of dextrose-containing dialysis fluids. **B**

F. In CKD people with GFR between 15–60 mL/min and < 15 mL/min, prompt adjustments with a reduction to 75% and 50% in insulin TDD respectively are often necessary. However, in individuals with GFR > 60 mL/min, no dose modifications may be required. **C**

G. Insulin therapy is preferred during the first 1–2 months after transplantation along with appropriate OADs. **B**

Future of insulins

The use of insulin therapy is crucial in the management of DM. SC injection is still the most common method for administering insulin. However, because of the short half-life of insulin, a person must endure many injections throughout the day to effectively regulate their blood glucose levels. This results in significant inconvenience and low compliance. Numerous initiatives have been attempted to enhance insulin administration, including the development of non-invasive routes, which mainly include buccal, oral, pulmonary, nasal, and trans-

dermal systems [95]. We are expecting the launch of newer insulins in India soon which are already available in the USA and Europe but not yet available in India.

On the other side, "biosimilar" refers to a protein molecule that is a perfect duplicate of already-existing insulin with the same amino acid sequence (except for small alterations in therapeutically relevant components) and no appreciable differences in efficacy and safety [15].

The advantage of biosimilar insulins is their low cost which makes them affordable for the majority. However, immunogenicity is a concern [96]. When switching from one kind of insulin to another insulin that are identical (biosimilar), it is recommended to carry out a dosage titration, always starting with a lower dose and up-titrating it to minimize hypoglycemia, with BGM [15].

Article information

Data availability statement

The initial stage was the development of recommendation statements following a comprehensive literature review using PubMed and other online resources for clinical studies, existing guidelines, review articles, consensus statements, and national and international standards on insulin therapy in adults with diabetes. The relevant data was retrieved and reviewed, recommendation statements were developed and compiled into a Microsoft Excel sheet.

While taking the American Diabetes Association (ADA), National Institute for Health and Care Excellence (NICE), European Association for the Study of Diabetes (EASD), The International Society for Pediatric and Adolescent Diabetes (ISPAD), American Association of Clinical Endocrinologists (AACE) guidelines and other peer-reviewed evidence-based guidelines and consensus statements into consideration, the expert panel comprising 16 practicing endocrinologists from the Association of Clinical Endocrinologists has drafted new recommendations with specific consideration for the Indian milieu keeping in mind the resources available to the general physician or a general practitioner.

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Authors contributions

Ravi Sankar Erukulapati: prime author; lead of the Consensus Group, coordinated the entire process, drafted recommendation statements for rounds 1, 2, and 3.

Ravi Sankar Erukulapati and Murali Ganguri participated in the drafting of recommendation statements for rounds 1, 2, and 3.

All authors participated in rounds 1, 2, and 3 of modified Delphi process.

All authors participated in writing up the Consensus document.

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Conflict of interest

The authors declare no conflict of interest.

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