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GUIDELINES

RSSDI consensus recommendations on insulin therapy in the management of diabetes

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Abstract

The Research Society for the Study of Diabetes in India (RSSDI) has regularly updated its Clinical Practice Guidelines on various aspects of diabetes. The pharmacotherapeutic management of diabetes involves a plethora of agents targeting different aetiopathogenic mechanisms administered orally or via injections as well as insulin. While most people with type 1 diabetes need complete insulin replacement therapy with multiple-daily subcutaneous injections of insulin or a continuous subcutaneous insulin infusion pump, patients with type 2 diabetes may also need insulin as and when needed, especially owing to the declining beta cell function due to the progressive nature of their diabetes. To date, various insulin regimens including basal-bolus, split-mixed, premix, and prandial therapy are available which can be individualized based on the patient profile though their prescription is often perceived as complex for management of diabetes, forming a major barrier in the acceptability of insulin. In order to provide physicians with a simple guidance on different aspects of insulin use including choosing the right insulin and regime to

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match the individual patient, the RSSDI for the first time has formulated this guideline on insulin therapy using simple algorithms for insulin initiation as well as titrations based on a systematic literature search of new clinical evidences on all aspects of insulin use. Insulin therapy is hereby proposed as easy to initiate and maintain, efficacious, and a safer option which when administered appropriately can almost mimic physiological insulin secretion in diabetic patients and help them achieve target glucose control and minimize complications while improving their quality of life.

Keywords Insulin · Diabetes · Premix · Basal · Regular insulin

Introduction

In 2017, diabetes mellitus has affected 425 million people globally, and without effective prevention and management, the number of people with diabetes is projected to rise to 629 million by 2045 [1]. India has become a diabetes capital of the Southeast Asian region, with an estimated 74 million people, aged 18–99 years, having diabetes and premature mortality of 50.7% (20–79 years) [2]. A population-based cross-sectional study estimating the national prevalence of diabetes and prediabetes in India reported an overall prevalence of 7.3% [3]. In 2019, the TIGHT study by Borgharkar and Das involving 55,639 eligible patients' records reported uncontrolled glycated hemoglobin (HbA1c) ≥ 7% in nearly 76.6% of patients. Sixty-two percent of these patients had HbA1c between 7 and 8% (53–64 mmol/mol). One-third of the study population had microvascular complications, predominantly neuropathy. Glycemic control from the combination of oral antidiabetic drugs (OADs) with or without insulin varied between 14.2% and 24.8% [4].

Although OADs remain the mainstay of treatment for early stages of type 2 diabetes mellitus (T2DM), insulin therapy becomes inevitable as the disease advances to sustain life. In India, it is estimated that about 4 of 10 patients with T2DM are using insulin, either alone or in combination with OADs [5, 6]. Proper insulin injection technique is also vital to achieving glycemic control by ensuring appropriate delivery to the subcutaneous tissues and avoiding complications [7]. Nonetheless, insufficient knowledge of insulin use can result in poor acceptance, adherence, and outcome of therapy [7].

The objective of this report is to develop a consensus for use of insulin therapy in the management of Indian diabetes patients based on critical review of scientific evidence published in peer-reviewed journals and clinical expertise and experience as shared by experts. It will provide an objective snapshot of consensus practices both in type 1 diabetes mellitus (T1DM) and T2DM regarding insulin initiation and titration, parameters to be monitored during therapy, use in special populations, management of adverse effects, and strategies to overcome the various barriers to support adherence to insulin therapy.

Methodology

A steering committee involving experienced diabetologists and endocrinologists across India across India was constituted by RSSDI. The steering committee deliberated and defined the scope of the recommendations. Four expert panels, each comprising of one steering committee member acting as a coordinator, and several national experts were formed. The panels reviewed all available evidence—national and international—to formulate the recommendations.

All the available scientific literature was reviewed. In paucity of published literature on various aspects, the panel formulated the recommendations on the basis of clinical acumen and experience, judgement, and consensus. These recommendations were then reviewed by the steering committee which was subsequently finalized by the writing group as a draft consensus document.

The Indian evidence published between 1990 and 2019 was used to decide on the analytical re-evaluation of recommendations proposed by RSSDI 2019. The relevant Indian literature was obtained from keyword-based searches of indexed literature including articles published in the *International Journal of Diabetes in Developing Countries* (*IJDDC*). Other relevant sources included *RSSDI Textbook of Diabetes* (third edition), *Journal of Association of Physicians of India* (JAPI), and the personal experience as shared by authors. In the absence of Indian literature, Asian/global evidence was considered.

Insulin secretion and physiology

Insulin is synthesized in the pancreatic beta cell as preproinsulin, which is then processed by proteolytic enzymes of the rough endoplasmic reticulum to proinsulin. This proinsulin is then transferred to the Golgi apparatus from where it is efficiently sorted into secretory vesicles. Conversion of proinsulin to insulin occurs in these secretory granules through prohormone convertases 2 and 3 and carboxypeptidase H, which is then secreted by exocytosis as shown in Fig. 1 [8, 9].

High-capacity glucose transporters (GLUT-1, GLUT-2, and GLUT-3 in humans) help in transporting the glucose into β cells and enable the rapid equilibration of extracellular and

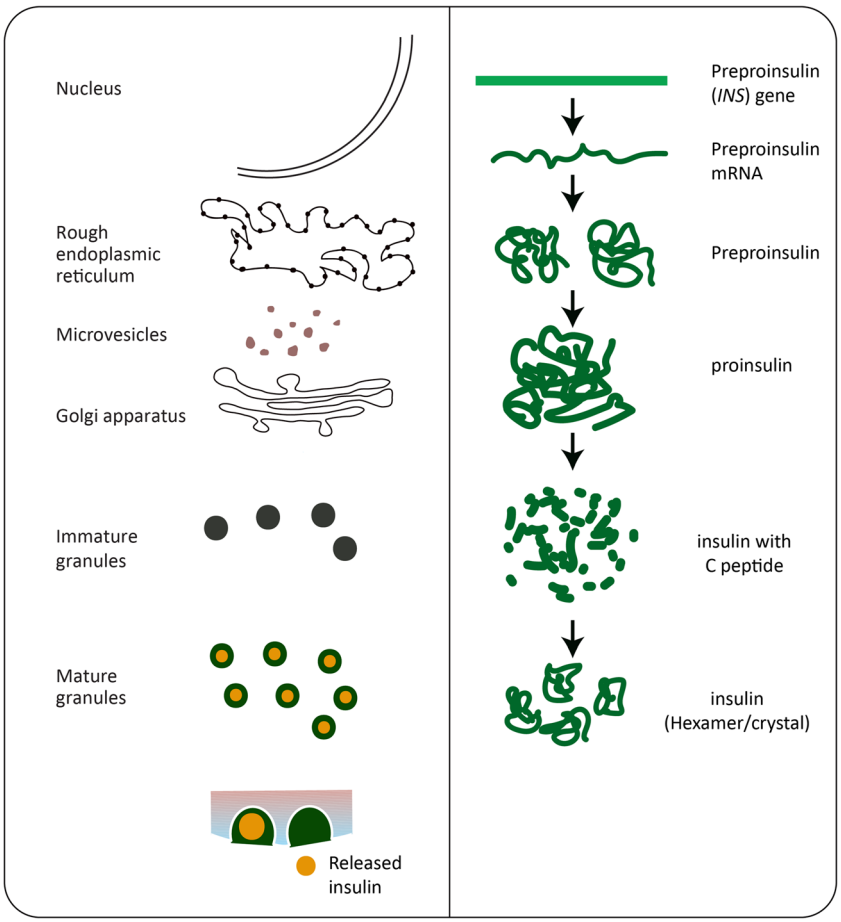

Fig. 1 The intracellular pathways of (pro) insulin biosynthesis, processing, and storage

intracellular glucose concentrations [10]. After entering the β cell, phosphorylation of glucose takes place with the help of glucokinase; this further acts as "glucose sensor" which couples the insulin secretion with the prevailing levels of glucose [11]. The glucose-induced insulin secretion from isolated islets (in vitro) forms a sigmoidal dose–response curve (Fig. 2a) which is determined primarily by the activity of glucokinase. Glucose concentration less than 5 mmol/L does not affect the rate of insulin release, and the rate of secretion increases progressively at extracellular glucose levels between

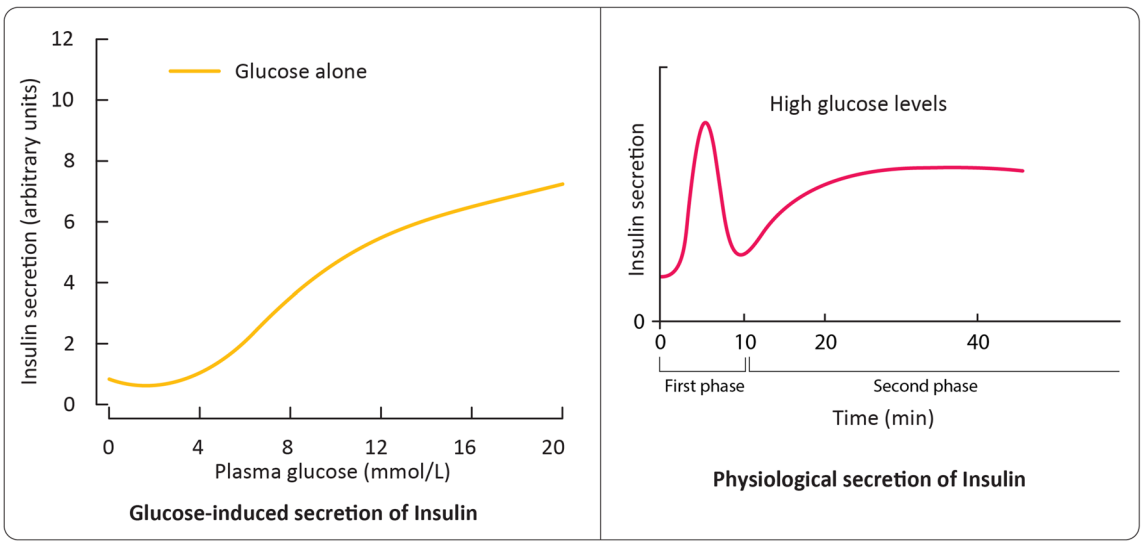

Fig. 2 Glucose-induced insulin secretion and release. **a** Glucose-induced secretion of insulin. **b** Physiological secretion of insulin

5 and ~ 15 mmol/L, with half-maximal stimulation at ~ 8 mmol/L [9]. In healthy individuals, insulin is secreted in a pulsatile manner into the portal circulation after an equal interval of 5 min as physiological insulin production by the pancreatic β cells [12]. Basal insulin production constitutes approximately half of the total daily insulin secretion and is responsible for controlling lipolysis and glycogenolysis. The remaining insulin secretion occurs after meal. The time taken from the response of insulin secretion to elevated glucose is characterized by a rapidly rising but transient first phase, followed by a maintained and prolonged second phase, as shown in Fig. 2b. This graphical representation of insulin secretion shows the biphasic secretion pattern of islets and also shows whether the insulin levels are measured after glucose load in humans or whether the secretory output from the perfused pancreas or isolated islets is assessed [9].

Insulin secretion in patients with diabetes

After it was reported by Lang and Bingley that healthy individuals have oscillating plasma insulin levels, patients with T1DM and T2DM were indicated to have an altered pattern of pulsatile insulin release [12, 13]. Patients with T2DM can be characterized by increased insulin resistance with decreased glucose clearance rate, manifesting as a decreased and impaired early-phase insulin secretion while patients with T1DM have an absolute or near absolute deficiency of insulin secretion [14].

The insulin receptor and mechanism of action

The receptor tyrosine kinase is functionally similar to insulin-like growth factor-1 receptor and helps in transmitting the action of insulin (Fig. 3) [15]. The number of receptors can vary from as few as 40 per cell on the erythrocytes that are relatively insulin-insensitive to up to 300,000 per cell on adipocytes and hepatocytes which are highly sensitive to insulin.

The expression of insulin receptors on almost all the mammalian cell types explains the broad range of biological responses to insulin. Tissues such as liver, fat, and skeletal muscle are considered critical for regulation of blood glucose (Fig. 4). Recent studies have also suggested that specific areas of the brain and pancreatic islet are an important target for insulin. The mechanism of action of insulin is anabolic, i.e., building muscles, and signaling of insulin helps in promoting the uptake, use, and storage of glucose, lipids, and amino acids. Insulin action further stimulates glycogenesis, lipogenesis, and protein synthesis and inhibits the breakdown of these compounds [16]. The metabolic effects of insulin such as inhibition of lipolysis or hepatic glucose production occur rapidly, within minutes of increasing concentration of plasma insulin; detectable increases in glucose clearance from the blood may take nearly an hour. Various factors that cause the inconsistency in the kinetics of insulin action include variable access to insulin receptors in different tissues, separate intracellular signaling pathways, and inherent kinetics of various processes controlled by insulin [16].

Exogenous insulins and its classifications

In India, the currently used insulins are either “human” insulins and/or their analogs. Insulin therapy mainly replicates the normal pattern of endogenous insulin secretion by supplying insulin at a baseline rate augmented by pre-meal insulin boluses. So, insulin therapies are comprised of basal insulin and

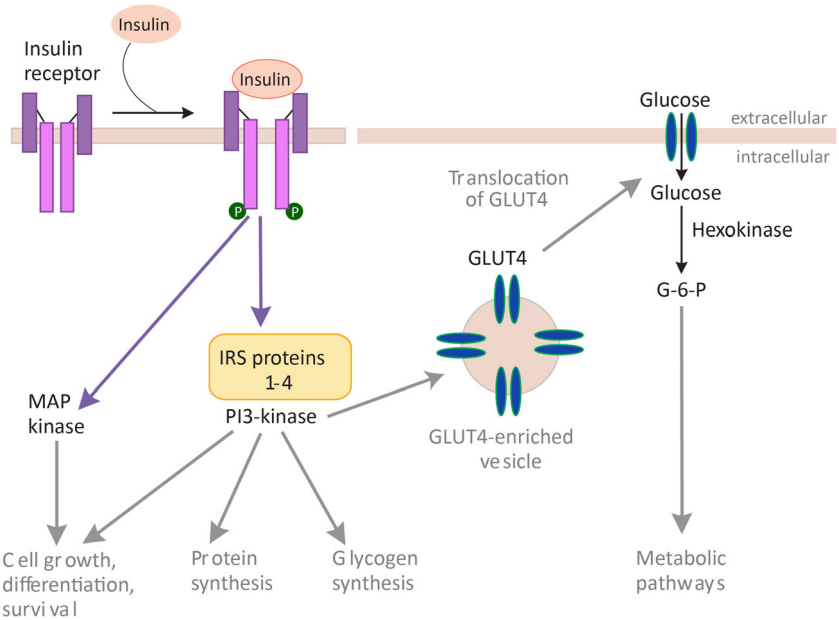

Fig. 3 Pathways of insulin signaling. IRS, insulin receptor substrate; MAP kinase, mitogen-activated protein kinase; GLUT4, glucose transporter type 4; G-6-P, glucose 6-phosphate; P13-kinase, phosphoinositide 3-kinase

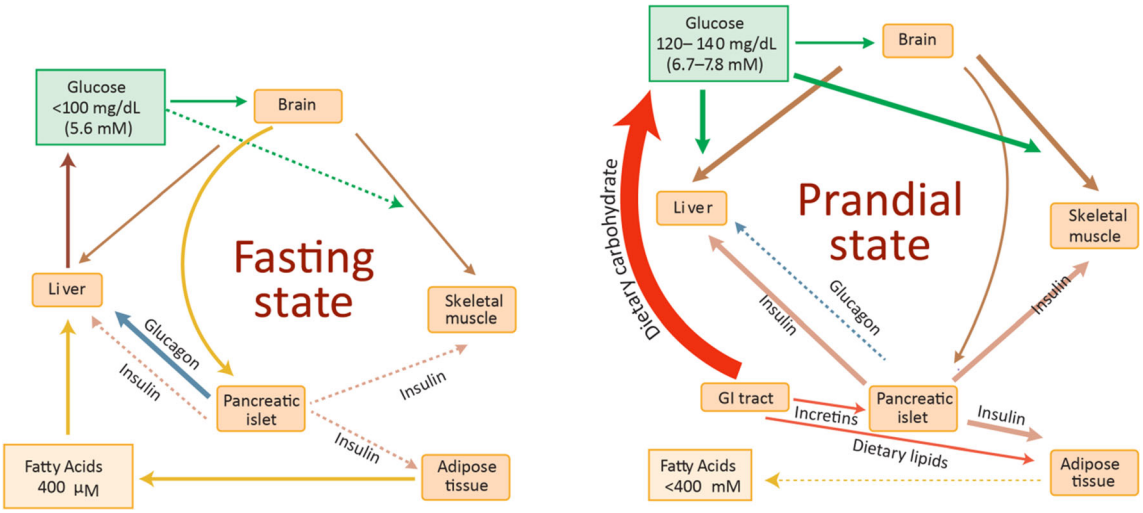

Fig. 4 Insulin, glucagon, and glucose homeostasis

bolus insulin dose (Fig. 5). Insulin analogs are categorized as rapid-, short-, intermediate-, and long-acting insulin preparations based on their pharmacokinetic (PK) properties. Rapid- and short-acting insulins are used as bolus doses and intermediate- and long-acting ones are used as basal doses [8].

A detailed PK classification is depicted in Table 1 based on onset of action, peak plasma concentration, and duration of action.

Basal insulins (intermediate- and long-acting insulins)

Currently, after the neutral protamine Hagedorn (NPH) (intermediate-acting insulin), the most frequently used basal insulins are the long-acting insulin analogs (glargine and detemir, etc.) followed by the second-generation basal insulin analogs namely insulin degludec and U300 glargine. In contrast to first-generation basal insulin analogs (glargine and detemir), insulin degludec and U300 glargine have a longer duration of action, stable profile, and documented lower instances of overall and nocturnal hypoglycemia. Insulin degludec has documented a 53% reduction in nocturnal hypoglycemia compared with U100 insulin glargine [17]. Although the first-generation basal insulin analogs provide an equivalent glycemic control, lower risk of hypoglycemia has been noticed with these preparations compared with NPH insulin [18, 19]. The PK features of injected or exogenous insulin are highly different compared with endogenous insulin secretion, which gets amplified to provide peak levels in response to a meal. Absorption of an insulin injection demonstrates a peak followed by trailing off, which increases the risk of hypo- or hyperglycemia depending on the level of insulin (Fig. 6). Different approaches have been used to retard absorption from the injection depot including varying the components of the insulin mixture in the pharmaceutical formulation [20]. One such example is NPH insulin that consists of a complex of insulin and zinc with protamine. This approach not only reduces its solubility but also extends its duration of action (12–18 h with a peak effect at around 4 h). Tailoring of insulin side chains (A or B chains) structure by replacing, deleting, or inserting of amino acids can also modify the PK profile of insulin as addition of two arginine units at B31 and B32 and substitution of asparagine by glycine at A21 results in

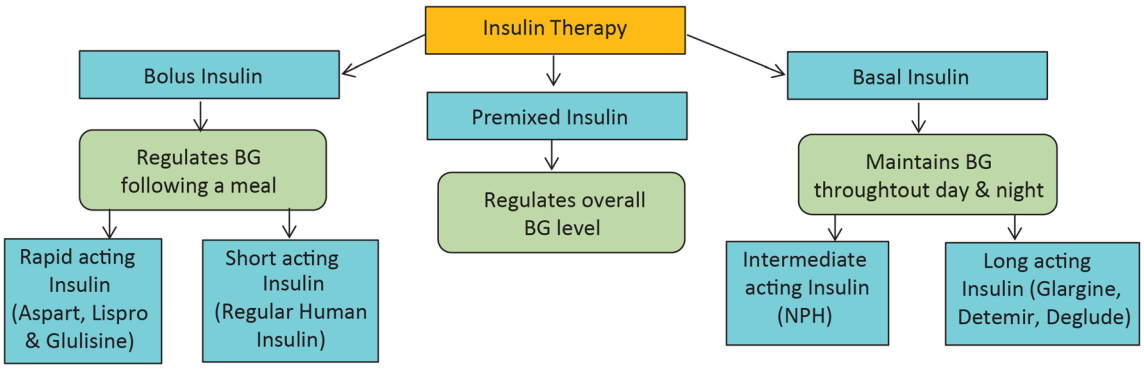

Fig. 5 Insulin therapy. BG, blood glucose; NPH, neutral protamine Hagedorn

Table 1 Structure and PK details of various insulins

Insulin		Alteration	Onset of action	Peak action time	Duration of action
Short-acting	Regular		~ 30 min	1.5–3.5 h	7–8 h
Ultra-rapid-acting insulin	Aspart (FIAsp)	L-Arginine (stabilising agent) and niacinamide (accelerated initial absorption after SC inj.) have been added	2.5 min	60 min	3–5 h
Rapid-acting insulin	Lispro	Reversal of amino acid proline at B28 and lysine at B29	~ 15 min	30–70 min	2–5 h
	Aspart	Replacing proline at B 28 with aspartic acid	10–20 min	1–3 h	3–5 h
	Glulisine	Replacing asparagine with lysine at B3 and glutamic acid with lysine at B29	10–20 min	~ 55 min	~ 6 h
Intermediate-acting	Isophane insulin; NPH	Neutral protaminated insulin	1.5–4 h	2.8–13 h	Up to 24 h
Long-acting	Glargine 100	Asparagine replaced with glycine at A21 and two arginine amino acids added at position B31 and B32	1–3 h	4 h (peak not pronounced)	Up to 24 h
	Glargine 300		6 h	No peak	Up to 36 h
	Detemir	Myristic acid acylation to the lysine residue on position B-29 and deletion of threonine from B30	1–2 h	3–9 h (peak not pronounced)	Up to 24 h
	Degludec	Deletion of threonine at B30 and addition of 16-carbon fatty acid to lysine at B29 via a γ-L-glutamic acid linker	0.5–1.5 h	No peak	Up to 48 h
Premixed human insulin	NPH/Regular 70/30	70% isophane insulin and 30% Regular insulin	30–90 min	1.5–6.5 h	18–24 h
	Human mixtard 50:50	Soluble insulin 50% and isophane insulin 50%	30–90 min	1.5–6.5	Up to 24 h
Premixed insulin analogues	ProLispro/Lispro 75/25	75% neutral protaminated insulin lispro and 25% insulin lispro	10–30 min	Dual	Up to 24 h
	ProLispro/Lispro 50/50	50% neutral protaminated insulin lispro and 50% insulin lispro	10–30 min	Dual	Up to 24 h
	ProAspart/Aspart 70/30	70% protaminated insulin aspart and 30% insulin aspart	10–20 min	Dual	Up to 24 h
	Novomix 50:50	50% soluble and 50% protamine-crystallised insulin aspart	5–15 min	Dual	Up to 16 h
Insulin co-formulation	IDegAsp (30/70)	70% insulin degludec and 30% insulin aspart	5–15 min	30–90 min	> 24 h
	LixiLan	Each mL contains 100 units insulin glargine and 33 mcg lixisenatide	This fixed ratio has no impact on the PK of IGlar. After SC administration, IGlar showed no pronounced peak and median tmax of lixisenatide was in the range of 2.5 to 3.0 h		
	IDegLira (100/3.6)	Each mL contains 100 units of insulin degludec and 3.6 mg of liraglutide	The PK of IDeglu and liraglutide were not affected when administered as fixed ratio (100/3.6). Steady-state concentrations of IDeglu and liraglutide are reached after 2–3 days of daily administration		

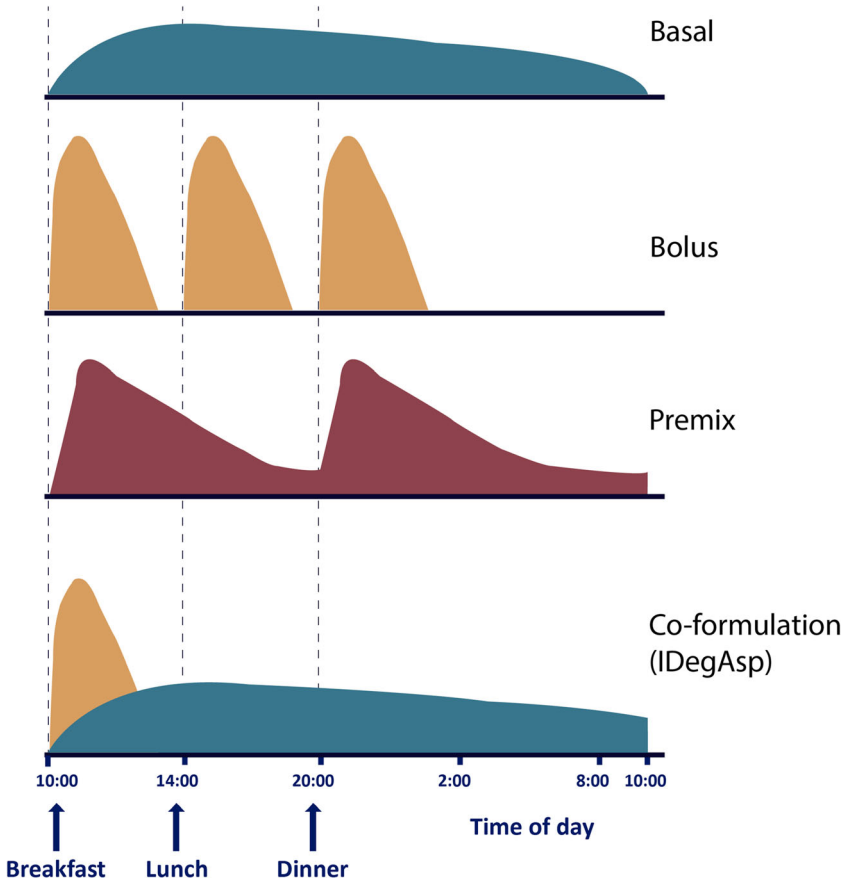

Fig. 6 Action profile of insulin

shifting the isoelectric point making it less soluble at physiological pH [21, 22]. Mechanisms contributing to the sustained duration of action are shown in Table 2 [23].

Insulin co-formulations

Insulin degludec/insulin aspart (IDegAsp) is a first soluble co-formulation comprising of both basal and bolus insulin components with favorable PK profile as compared with previously available biphasic insulin preparations. IDegAsp has shown noninferiority in controlling HbA1C as compared with currently available basal and premixed insulins in once- and twice-daily dosing. Additionally, the risk of hypoglycemia is also reduced. The favorable pharmacological profile is seen as offering distinct clinical benefits over the conventional premixed insulin suspensions [24].

Numerous studies are currently underway that will confirm the efficacy and safety of combining basal insulin to GLP1R agonists. This combination is expected to provide enhanced glycemic control by regulating both fasting and postprandial plasma glucose albeit to a lesser extent. This combination helps promote weight loss and has a lower risk of hypoglycemia (Table 1).

Bolus insulins/rapid-acting/prandial insulins (insulin lispro, insulin aspart, and insulin glulisine)

The rapid-acting insulin was developed to provide more rapid absorption than regular human insulin, thereby reducing postprandial glucose excursions effectively. Four rapid-acting insulin analogs, namely lispro, aspart, glulisine, and FiAsp (faster-acting aspart), have so far been developed and introduced into the clinical practices. These analogs can be administered before meals to mimic the endogenous postprandial insulin surge (Fig. 6). All these analogs were developed by making modifications in the amino acid sequence. These modifications decreased the tendency of insulin chains to form dimers and hexamers, thus increasing their bioavailability [21].

Table 2 Mechanisms contributing to sustained duration of action for basal insulins

Insulin	Glargine	Detemir	Degludec
Mechanism contributing to sustained duration of action	Micro-precipitate formation	Binds albumin	Multi-hexamer formation at the site of injection

Premix insulins (including biphasic insulins)

Premixed insulins, consisting of rapid- or short-acting and intermediate- or long-acting insulins, were developed to take care of both the basal and meal-related insulin requirements and, at the same time, reduce the number of daily injections. Indeed, the concept of the ideal formulation to more closely mimic physiological endogenous insulin secretion had not been possible until recently, as the basal insulin could not be mixed with other insulins. Therefore, in premixed insulin preparation, a part of rapid-acting insulin has protamine to convert it to intermediate-acting insulin. This challenge of mixing has been conquered by developing an IDegAsp as the first soluble co-formulation. Biphasic human insulin contains various proportions of insulin with a protamine counterpart. The most commonly available premixed insulins including biphasic human insulin (30% regular human insulin and 70% protamine regular human insulin), biphasic insulin lispro (Humalog Mix25; 75 protaminated/25 normal and Humalog Mix 50; 50 protaminated/50 normal) and biphasic insulin aspart 30 (BIAsp 30; 70 protaminated/30 normal). Compared with human premixed insulins, the biphasic insulin analogs have a more rapid onset of action (5–15 min) with an earlier peak observed in 1–2 h for the first component and a relatively steady second component lasting up to 16 h [25, 26]. These features result in improved PD effect, with clinically favorable biochemical and physiological antihyperglycemic effects in vivo (Fig. 6) [27].

Choosing the right insulin and individualizing therapy for adults with T1DM

Insulin should be initiated immediately in people with newly diagnosed T1DM. This requires not only insulin regimen selection but also comprehensive diabetes education. Recent guidelines from the *American Diabetes Association* (ADA) recommend the use of multiple daily injections (MDIs) of prandial and basal insulin, or continuous subcutaneous insulin infusion (CSII) pump to treat most people with T1DM [28]. These guidelines also suggest the use of rapid-acting insulin analogs to reduce hypoglycemia risk. Patient education should be encouraged to optimize prandial insulin doses to expected nutritional carbohydrate intake, pre-prandial blood glucose levels, and anticipated physical activity [28]. The consensus evidence-based guidelines for insulin therapy in Indian patients with T1DM recommend the use of a basal-bolus regimen as the most preferred regimen [29]. A practical algorithm for managing T1DM is shown in Fig. 7.

Both basal-bolus injection therapy and CSII are considered the standard of care for patients with T1DM. The insulin regimens should be tailored, taking into account the individual's age, general health, lifestyle, treatment goals, hypoglycemia awareness status, adherence to treatment, and ability for self-management. Social and financial aspects also should be considered.

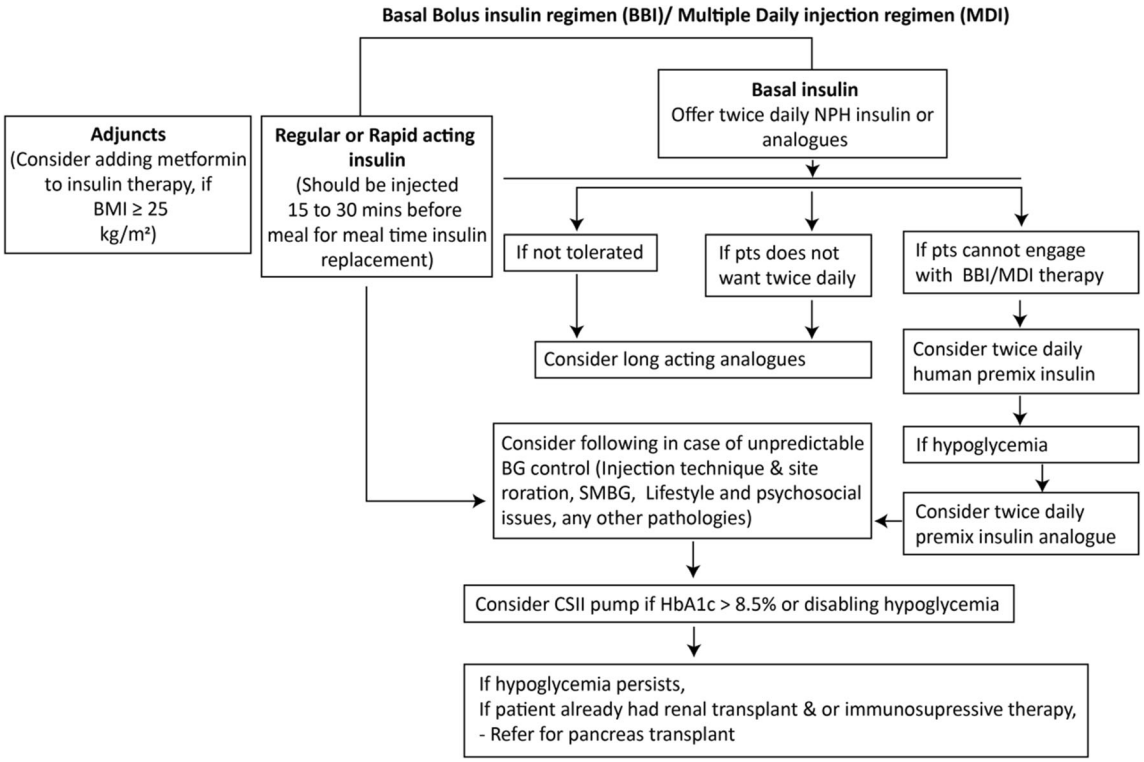

Fig. 7 Algorithm for managing T1DM. BBI, basal-bolus insulin regimen; MDI, multiple daily injection regimen; CSII, continuous subcutaneous insulin infusion; HbA1c, hemoglobin A1c; BMI, basal metabolic index; NPH, neutral protamine Hagedorn

Conventional insulin regimen

Conventional insulin therapy involves injecting insulin once or twice a day. Most of the people with T1DM used standard mixtures of short-acting and long-acting insulin preparations for injecting insulin as this therapy did not usually require daily adjustments in insulin dose. The goals are to improve symptoms of hyperglycemia and ketonuria and maintain normal growth, development, and ideal body weight as well as freedom from severe or frequent hypoglycemia [30]. Evidence derived from studies that compared various insulin regimens for T1DM is presented below (Table 3) [31–35].

Multiple daily injections or basal-bolus insulin regimen

Intensive insulin therapy involves three or more insulin injections per day or insulin pump therapy. The goals are to provide better glycemic control and reduce the development and progression of microvascular and macrovascular complications [8]. Evidence derived from studies that compared various insulin regimens for T1DM is presented below (Table 3) [36–39].

Establishing a total daily dose of insulin

The first step of initiating the treatment with insulin in patients with newly diagnosed T1DM includes establishing a total daily dose, insulin sensitivity factors for correction doses, and insulin to carbohydrate ratio. This dose can vary from 0.3 to 1.5 units/kg/day, depending on the individuals. However, a good initial dose is ~ 0.5 units/kg/day. After determining the total daily dose (TDD) of insulin, it is divided by half which establishes the basal and bolus requirements. According to the thumb rule, the basal insulin should be about half of TDD of insulin, and the mealtime insulin should make up the other half.

For example, if a person is weighing 50 kg, the typical TDD of insulin would be 50 kg × 0.5 units/kg = roughly 25 units/day. The basal insulin dose would be roughly 12 units and bolus insulin total would be 12 units (divided among three meals, see below).

U-100 glargine and detemir should be administered once or twice daily as they are long-acting insulin analogs whereas insulin degludec or U-300 insulin glargine can be administered once a day as they are ultra-long-acting insulin analog [40].

Using prandial insulin

Establishing insulin to carb ratio

In T1DM, using basal and prandial analogs together helps in achieving the greatest therapeutic benefit. The administration of pre-meal insulin requires the patient to know their present blood glucose level and the estimated amount of carbohydrates present in the meal. Initially, the amount of prandial insulin can be determined by approximating the percentage of calories consumed at each meal. Later on, patients can alter the prandial dose by estimating the carbohydrate component of each meal or a snack [41, 42].

The initial dose of insulin administered in patients with T1DM is 1 unit of rapid-acting insulin for every 15 g of carbohydrates. The carb to insulin ratio can vary from 1 unit for every 5 to 30 g of carbohydrate. To estimate the carb ratio, the "500 rule" can be used:

$$500/\mathrm{TDD} = \textit{grams of carbohydrate covered by 1 unit of insulin}.$$

Example A person who takes a total of 40 units of insulin/day (both basal and prandial combined) will need 1 unit of rapid-acting prandial insulin for every 12.5 g carbohydrate (500/40 = 12.5 g of carbohydrate covered by 1 unit of insulin, using the above formula).

Calculating the carb ratio (alternative method) Sum of all carbohydrates consumed in a day/total units of prandial insulin taken that day, using an average over 3 days.

Prandial insulin can be skipped/reduced in the following conditions:

- Using extra carbohydrates to raise low blood sugars or cover increased physical activity
- If the recent dose is taken within 1–2 h
- Nausea or vomiting

Calculating correction dose/insulin sensitivity factor

Insulin sensitivity factor or correction dose is referred to as the number of milligrams per deciliter (mg/dL) by which blood sugar levels fall when a person takes 1 unit of insulin. The "1500 rule" for short-acting regular insulin (divide 1500 by daily insulin dose for mg/dL, 83 for mmol/L) and "1800 rule" for rapid-acting insulin (divide 1800 by daily insulin dose for mg/dL, 100 for mmol/L) should be followed. These methods are widely used to calculate "the correction factor" or "insulin sensitivity factor," i.e., the glucose-lowering effect of 1 unit of insulin [41, 43]. The correction dose can be used for elevations of blood glucose that occur in-between the meals. And can be utilized in patients who had not taken an injection of rapid-acting insulin over the past 2–4 h (insulin on-board).

Target glucose The insulin sensitivity factor (ISF) helps in achieving individualized blood glucose targets.

Table 3 Summary of clinical evidences for insulin regimens in management of T1DM

Author	Design/population	Objectives	Regimens	Results
Conventional regimens				
De Leeuw et al., 2005	12-month multicentre, open-label, parallel-group study	IDet vs. NPH, with insulin aspart at mealtimes	Total 308 patients (2:1) received insulin detemir or NPH insulin before breakfast and dinner twice daily	• No difference between treatments in terms of HbA(1c), FPG, or 9-point blood glucose profiles • 32% lower risk of nocturnal hypoglycemia with IDet ($p = 0.02$) • Mean BW was lower with IDet vs. NPH ($p < 0.001$).
Birkeland et al., 2011	16-week, randomized, open-label trial	IDeg(A) vs. IDeg(B) vs. insulin glargine (IGlar), with mealtime insulin aspart	SC injections of IDeg(A) (600 μmol/L; $n = 59$) vs. IDeg(B) (900 μmol/L; $n = 60$), vs. insulin glargine (IGlar; $n = 59$), all given once daily in the evening	• No difference between IDeg(A), IDeg(B), and IGlar in terms of HbA1c (7.8 ± 0.8%, 8.0 ± 1.0%, and 7.6 ± 0.8%), and FPG (8.3 ± 4.0; 8.3 ± 2.8; and 8.9 ± 3.5 mmol/L, respectively) • Compared with IGlar, risk of hypoglycemia • 28% lower with IDeg(A) (RR, 0.72 [95% CI 0.52–1.00]) • 10% lower for IDeg(B) (RR, 0.90 [0.65–1.24])
Heise et al., 2012	Randomized single-center, parallel-group, double-blind trial	Insulin degludec (IDeg) vs. insulin glargine (IGlar)	54 subjects underwent a 24-h euglycemic glucose clamp on the 6th, 9th, and 12th days of treatment with 0.4 U/kg of IDeg or IGlar once daily.	• Compared with IGlar, the day-to-day variability in glucose-lowering effect was four times lower with IDeg (AUC (GIR, 0–24 h, SS), CV 20% vs. 82%) and for the last 22 h (AUC (GIR, 2–24 h, SS))
Tricco et al., 2014	Systematic review and network meta-analysis	Long-acting insulins	Review of 39 studies involving 27 RCT and 7496 pts for safety, efficacy and cost-effectiveness of long-acting insulins	• IGlar OD, IDet OD, and IDet OD/BD significantly reduced HbA1c compared with NPH OD (26 RCTs, − 0.39%, 95% CI − 0.59 to − 0.19%; − 0.26%, − 0.48 to − 0.03%; and − 0.36%, − 0.65 to −0.08%; respectively) with less risk of hypoglycemia and weight gain
Laranjeira et al., 2018	Systematic reviews and update existing reviews	LAIAs vs. NPH	11 systematic reviews with 25 trials	• Compared with NPH, LAIAs were more efficacious in reducing • Nocturnal hypoglycemia episodes (RR 0.66; 95% CI 0.57; 0.76) • A1C (95% CI 0.23; 0.12) • No significance was found related to severe hypoglycemia (RR 0.94; 95% CI 0.71; 1.24)
Multiple daily injections or basal-bolus insulin regimen				
Chatterjee, 2007	36-week randomized open-label two-period crossover trial	IGlar vs. NPH with insulin aspart at mealtimes	60 pts received 16 weeks' treatment with either once-daily IGlar or twice-daily NPH insulin after 4-week run-in	• Compared with NPH, IGlar showed significant reduction in HbA1c (8.07% vs. 8.26%; $p = 0.04$) and FPG ($p = 0.002$) • No differences in hypoglycemia rate ($p = 0.63$), weight ($p = 0.45$), or lipid profile ($p = 0.18$) • Patient satisfaction was greater with IGlar (DTSQ, $p = 0.001$)
Cemeroglu, 2013	Prospective treatment, open-label, crossover study	Insulin glulisine alternating with aspart prior to a prescribed breakfast	Thirteen prepubertal children received insulin glulisine alternating with insulin aspart with a fixed amount of carbohydrate (45, 60, or 75 g) for 20 days	• Compared with aspart, mean increase in 2-h PPBG was higher in glulisine (+ 98.6 ± 66.9 vs. + 113.5 ± 65.2 mg/dL; $p = 0.01$) • BG remained higher at 4 h (glulisine 141.9 ± 36.5 mg/dL, aspart 129.0 ± 37.0 mg/dL) ($p = 0.04$).
Yanagisawa et al., 2014	Prospective, open-label, 24-week study	Replacement of short-acting insulin with glulisinealongwithIGlar	In 59 pts (49 T1DM and 10 T2DM) with uncontrolled BG, short-acting insulins [aspart ($n = 19$), lispro ($n = 37$) and regular human insulin ($n = 3$)] were replaced with insulin glulisine	• Switching to glulisine insulin for 24 weeks significantly decreased level of HbA1c, prevented vascular damage, and improved treatment satisfaction
Agesen et al. 2016	2-year investigator-initiated multicentre, prospective, randomized, open, blinded endpoint (PROBE) trial ($n = 114$)	Reduction of non-severe hypoglycemia events with insulin analogues in patients with recurrent severe hypoglycemia	Using a balanced crossover design, 114 patients were randomized to basal-bolus therapy based on analogue (IDet/Asp) or NPH/regular human insulins	• Analogue-based treatment resulted in a 6% (2–10%; $p = 0.0025$) overall relative risk reduction of non-severe hypoglycemia
Continuous subcutaneous insulin infusion or insulin pump therapy				
Benkhadra, 2017	A systematic review and meta-analysis	CSII vs. MDIs	Review of 25 RCTs comparing CSII and MDIs for their effect on HbA1c, and hypoglycemic events	• Compared with MDIs, CSII showed significant reduction in HbA1c (MD 0.37; 95 % CI, 0.24–0.51)
Wan, 2018	The DIAMOND Randomized Trial	CSII vs. continuing MDI in adults using CGM	75 adults using CGM were randomized to CGM plus CSII or CGM + MDI (control) and surveyed at baseline and 28 weeks.	• Compared with controls, CGM + CSII group showed a significant reduction in QoL from baseline (− 0.02 ± 0.05 difference in difference [DiD]) • Total per-person 28-week costs were $8272 (CGM + CSII) vs. $5623 (CGM + MDI)
Qin, 2018	A meta-analysis of RCTs	CSII vs. MDI	CSII vs. MDI in children with T1DM	• Compared with MDI, CSII showed significantly reduction in HbA1c ($p = 0.007$) • No difference between groups in HbA1c change, TDD, TDD change, and incidence of ketoacidosis and severe hypoglycemia
Blair, 2019	Pragmatic, multicenter, open-label, parallel-group, RCT and economic evaluation	CSII vs. MDI	Start treatment with CSII or MDI within 14 days of diagnosis	No difference between CSII and MDI (60.9 mmol/mol vs. 58.5 mmol/mol, $p = 0.09$) in achieving HbA1c thresholds

Table 3 (continued)

Author	Design/population	Objectives	Regimens	Results
Artificial pancreas				
Karageorgiou, 2018	A systematic review and network meta-analysis	Evaluation of closed-loop (CL) systems in the glycemic control	Review of 25 RCTs comparing glycemic control in CL (either single- or dual-hormone) with CSII	• The CL group was associated with significantly - Higher percentage of time spent in the target glycemic range (mean (SD), 67.59% (8.07%) - Lower percentages of time in hyperglycemia (MD 3.01%, 95% CI [1.68, 4.34%]) and hypoglycemia (MD 0.67%, 95% CI [0.21, 1.13%]) • Mean glucose was also decreased in the CL group (MD 0.75 mmol/L 95% CI [0.18–1.33]) • Higher time was spent in the near normoglycemic range (3.9–10.0 mmol/L) with artificial pancreas use, both - Overnight (weighted mean difference 15.15%, 95% confidence interval 12.21 to 18.09%) and - Over a 24-h period (9.62%, 7.54 to 11.7%)
Bekiari, 2018	Systematic review and meta-analysis of RCTs 40 studies with 1027 participants)	Evaluation of artificial pancreas treatment	Artificial pancreas system vs. type of insulin-based treatment	Time spent in range was 70–250 mg/dL, 94.7%; in range 70–180 mg/dL, 82.6%; < 70 mg/dL, 4.1%; and < 50 mg/dL, 0.2% During the last night, the time spent in range was 70–250 mg/dL, 95%; in range 70–180 mg/dL, 87.7%; < 70 mg/dL, 5.0%; and < 50 mg/dL, 0.0%. No severe hypoglycemia and serious adverse events were reported
Sánchez-Peña, 2018	36-h pilot study	Feasibility of artificial pancreas strategy	To validate the ARG algorithm, five T1DM subjects were enrolled	

For example: If a person takes 60 units per day and has a blood glucose of 240 mg/dL before the meal, an extra dose of 3 units will lower the blood glucose level by an additional 90 mg/dL with rapid-acting insulin or 75 mg/dL with short-acting insulin. In the same way, units can be subtracted from the pre-meal dose if the blood glucose level is low.

1. ISF = 1800/60 (TDD) = 30; 1 unit of rapid-acting insulin will decrease glucose by 30 points; 1500/60 = 25; 1 unit of short-acting insulin will decrease glucose by 25 points.
2. 240 mg/dL (actual glucose level) − 120 mg/dL (target glucose level) = 120; this is the excess glucose, that is, the value that is above target and that needs to be corrected.
3. 120/30 (ISF) = 4 for rapid-acting; 120/25 = 4.8 for short-acting insulin; dividing the excess glucose by the ISF will provide the amount of correction insulin units that are required to bring down the glucose to target.

Putting it all together—combining the carb ratio and ISF

Combining the carbohydrate load and ISF will enable patients to appropriately target their pre-meal glucose.

For example: An individual with a carb ratio of 1:10 and ISF of 1 unit/40 mg/dL, prior to a meal of 50 g carbohydrates and a pre-meal blood glucose of 210 mg/dL and target of 120 mg/dL, would take the following steps to administer the appropriate amount of prandial insulin as follows:

1. To cover carbohydrate intake: 50 g/10 g per unit = 5 units
2. Correction dose: 210 mg/dL (actual glucose) − 120 mg/dL (target glucose) = 90 mg/dL. ISF is 90/40 = 2.25 units to correct.
3. Total amount of prandial insulin: 5 (routine dose) + 2.25 (correction) = 7.25 units

Insulin titration and pattern adjustments

The most important aspects of diabetes management are reviewing blood glucose and recognizing patterns that will allow timely and appropriate adjustments in insulin dose, food intake, and managing physical activity. Recognizing patterns can be done by using tools such as self-monitoring of blood glucose (SMBG) with information obtained through download software or logbooks and continuous glucose monitoring (CGM) data [40, 43].

Continuous subcutaneous insulin infusion or insulin pump therapy

An external pump-based CSII results in better glycemic control as compared with MDIs of insulin allowing greater flexibility in routine activities. Modern-day insulin pump therapy can effectively address the disadvantages of inflexibility [44]. Pieces of evidence that compared CSII and MDI for T1DM are presented below (Table 3) [45–48].

The basal profile in the insulin pump replaces the use of basal insulin in the pump. Basal rates are programmed to deliver the

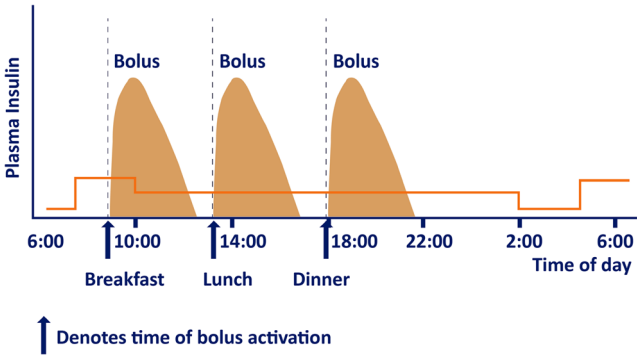

Fig. 8 Bolus and basal insulin infusion scheme in CSII

same rapid-acting insulin continuously in the background. The pre-prandial bolus dose serves the same purpose as normal insulin injections of insulin lispro, insulin aspart, or insulin glulisine. Multiple basal infusion rates and doses ranging from 0.025 to 35.0 units/h (frequently ranging from 0.4 to 2.0 units/h) can be infused using pumps. This is specifically useful to meet non-prandial insulin demands, though it is unlikely that the average patient will require more than 2 or 3 different rates (Fig. 8) [40, 43].

Fundamental differences between CSII and MDI

Titration of basal doses Practically speaking, the most important aspect of insulin dosing is to provide the correct amount of basal rate. Incorrect basal dosing leads to suboptimal bolus doses and the correction doses. Too high basal dosing is the commonest error observed in CSII therapy which results in hypoglcemia even with the smallest of correction doses. The flexibility of dosing and titration of basal doses is one of the greatest advantages of CSII [40, 43].

Depending on each patient's needs, the basal dose can be titrated throughout the day. This is usually done in a systemic manner using the "basal checks" approach. The following conditions such as last meal and/or insulin bolus should have occurred at least 4 h prior to starting the assessment; fat and protein restriction in the last meal and avoiding exercise and alcohol should be met before performing the basal check.

Additionally, assessment should not be performed if there is a prior hypoglycemic episode earlier in the day or there is an intercurrent illness [40].

Nighttime basal rate As a best practice, initiation should be done by addressing the overnight basal rate. A bedtime glucose range within the target is the pre-requisite for performing the overnight basal assessment. Any nutritional intake is restricted and the patient is asked to measure glucose levels at bedtime, at midnight, at 3 AM, and upon awakening. This is done to assess for changes in glucose profile (the use of a CGM obviously makes this exercise much easier). Additionally, any hypoglycemic symptoms also warrant the checking of blood glucose levels. The assessment is stopped in case of hypoglycemia or when glucose level rises above the target. A variation of ≤ 30 mg/dL in glucose levels on either side from bedtime to morning (upon awakening) is usually acceptable. However, glucose changes > 30 mg/dL warrant adjustments in basal rates which are generally in the range of 10–20% in insulin dose 2 h before the observed rise or fall in glucose levels. In general, a change in a basal dose takes 2 to 4 h to result in a change in blood glucose [40, 49].

Daytime basal rates A skipped mealtime period (pre-breakfast to pre-lunch, pre-lunch to pre-dinner, and pre-dinner to bedtime) is evaluated to check the day time basal rates. For instance, to check the "pre-breakfast to pre-lunch" time segment, breakfast is skipped following which glucose levels are checked at 1–2-h intervals for the duration of that time segment. Any hypoglycemic symptom also mandates the checking of glucose levels.

The same recommendations regarding changes in glycemic levels requiring insulin dose adjustments described for the overnight basal assessment apply here [40, 49].

Tracking of insulin on-board

Accurate tracking of insulin on-board using the pump is one of the major differences between CSII and MDI. If done correctly, this plays a major role in preventing insulin stacking [40, 50].

Insulin dose calculator

The insulin pump facilitates the setting of insulin to carbohydrate ratios and insulin sensitivity with corresponding target glucose values can be fixed and changed as and when required. Based on the glucose levels and anticipated carbohydrate amount to be consumed entered by the patient, the insulin pump calculates the insulin dose. This again is a big advantage over MDI which requires manual calculations to arrive at an optimal dose [40, 50].

Modifications to bolus delivery

Individual bolus doses that are administered over a slightly extended period can be obtained by appropriately programming the pumps. Patients with delayed gastric emptying as seen in gastroparesis or those on pramlintide can be benefitted from this feature of CSII [40, 50, 51].

Temporary basal rates

The insulin pump also facilitates the setting of the temporary basal rates which are required in certain situations. Intercurrent illness—requiring an increased insulin requirement or alternatively during exercise—requiring a reduction in insulin dose can be managed by setting temporary basal rates [40, 50].

Sensor-augmented insulin pump therapy

The sensor-augmented insulin pump (SAP) is an insulin pump with a CGM sensor that transmits the glucose readings to the insulin pump [52]. Based on the findings accumulated through 2013, The German Diabetes Association developed recommendations for use of CGM in T1DM. The Endocrine Society, the National Institute for Health and Care Excellence (NICE), the International Society for Pediatric and Adolescent Diabetes (ISPAD), the American Association of Clinical Endocrinologists/American College of Endocrinology, and the American Diabetes Association have published recommendations regarding clinical indications for use of CGM [53]. In 2016, El-Laboudi et al. reported that the use of CGM resulted in a dramatic and significant reduction in both HbA1c and mean glucose with highly significant improvements in hypoglycemia [54]. Mazze indicated that one needs about 15–30 days of CGM to obtain a stable pattern for the ambulatory glucose profile [55, 56]. Dunn and Crouther also reported that 14 days provides a good snapshot [57]. Xing et al. recommended the use of at least 12–15 days of data to ensure that results would be correlated with results based on a 3-month study to characterize the overall level of glycemic control, mean glucose, coefficient of variation of glucose (%CV), and percentages of glucose values within the hypoglycemic, hyperglycemic, and target ranges [58].

Moving close to the artificial pancreas

In patients with T1DM, a newer concept of an artificial pancreas, or closed-loop (CL) system, can be helpful. This technology works to deliver insulin in response to blood glucose levels. The closed-loop system works by integrating three distinct systems which work in close coordination to maintain euglycemia: (1) CGM sensor that measures blood glucose levels and sends data to a computer; (2) an algorithm that calculates the amount of insulin needed and instructs the pump to deliver it; (3) an insulin delivery device, such as an insulin pump. This enables minimum human input which removes subjectivity from the treatment regimen. Numbers of evidences evaluated the artificial pancreas, or "closed-loop (CL) system," for T1DM is presented below (Table 3) [59–61].

Non-insulin treatments for T1DM

T1DM mandates intensive insulin therapy; however, hypoglycemia and weight gain are often limiting factors in achieving glycemic targets in these patients. The use of pharmacological agents that are conventionally used in T2DM as an adjunct in T1DM has been explored to limit the side effects seen with insulin-based regimens. However, except for pramlintide, these adjunctive agents have not yet gained regulatory approval. Table 4 presents the injectable and oral glucose-lowering drugs that have been explored for their efficacy as adjuncts to insulin treatment of T1DM [62–67].

Recommendations from RSSDI for insulin therapy in patients with T1DM

- MDIs of prandial and basal insulin or CSII have proved to be effective and safe treatment for people with T1DM.
- Basal-bolus insulin therapies are considered as the standard regimen for the management of diabetes in T1DM.
- Basal insulin dosage is estimated based on weight and is normally initiated at 10 U or 0.1–0.2 U/kg/day and then up-titrated based on glycemic value, with typical doses ranging from 0.2 to 1.0 units/kg/-day.
- Regular insulin should be added for postprandial glucose control. Rapid-acting insulin analogs also can be used as it reduces hypoglycemia risk.
- Premixed insulin analogs help in reducing the HbA1c levels, controlling the PPG levels, and can also be used in adolescents in case of unavailability of other insulins.
- Individuals with T1DM should be educated regarding matching prandial insulin doses to carbohydrate intake, pre-meal blood glucose levels, and anticipated physical activity.

Sick day management for patients with T1DM

The insulin requirements usually increase during acute illness. Following such an increase, blood glucose monitoring frequency should also be increased. Patients may administer rapid-acting insulin every 2 to 4 h based on their glucose levels. Ketone testing can help to manage patients with severe vomiting or hyperglycemia. Recognizing the early signs and symptoms of diabetic ketoacidosis (DKA) is important to prevent it. If it is suspected, patients and/or caregivers should contact their physician as soon as possible.

Recommendations from RSSDI for sick day management for patients with T1DM

- In times of illness and decreased oral intake, advise the patient the following:
  - o Do not omit insulin.
  - o Frequent blood glucose monitoring at least every 3–4 h and often every 1 to 2 h (in critically ill patients) is essential.
  - o In patients experiencing acute illness, aim for a blood glucose levels between 140 and 180 mg/dL (8 and 10 mmol/L) and blood ketones should be below 0.6 mmol/L.
  - o The insulin dose often needs to be decreased when there is gastroenteritis due to limited oral intake and/or malabsorption to prevent hypoglycemia; however, one must ensure adequate basal insulin delivery to prevent hyperglycemia and hyperketonemia due to insulin deficiency.
  - o Hypoglycemia with hyperketonemia, which may occur in the setting of GI illness or starvation, requires administration of insulin along with carbohydrate intake.
  - o Maintaining hydration is essential in every patient with diabetes during an acute illness; oral fluids with or without sugar should be consumed depending on the glucose level; consider timely initiation of IV fluids if the patient is unable to drink.

Choosing the right insulin and individualizing therapy for adults with T2DM

When to start insulin in patients with T2DM

Insulin therapy may be indicated for those T2DM patients who failed to achieve glycemic targets with current OADs, or cannot tolerate current OADs, or those that need a more flexible therapy. Short-term use of insulin is also indicated in acute illness or surgery, pregnancy, and glucose toxicity. Insulin therapy as initial treatment may be indicated for those who present with hyperglycemic symptoms (polyuria or polydipsia) or any catabolic features (weight loss or ketosis). It should also be considered when optimal glycemic control cannot be achieved in patients with stressful situations such as acute myocardial infarction, stroke, acute infections, tuberculosis, trauma, and other conditions requiring hospitalization [68].

Recommendations from RSSDI regarding situations when insulin therapy may be indicated or should be considered

- T2DM patients who fail to achieve glycemic targets with current OADs, or cannot tolerate current OADs, or those who need more flexible therapy
- When adequate glycemic control is not obtained, in patients with myocardial infarction, stroke, or decompensated hepatic or renal insufficiency, or those who had major surgery
- Acute hyperglycemia, DKA/hyperglycemic-hyperosmolar state/lactic acidosis
- Pregnancy and lactation
- Diabetes patients on steroid therapy
- Insulin therapy is indicated for a short period of time in cases of acute illness or surgery, and glucose toxicity

Advantages of early use of insulin in T2DM and newly diagnosed T2DM patients

Conventional stepwise therapy approach in T2DM involves addition of antidiabetic agents one-by-one in a sequential fashion to control glucose levels. This may expose T2DM patients to prolonged periods of hyperglycemia of even up to 8 years [69]. The progressive deterioration of pancreatic insulin secretory function was such that after 3 years, only about half of patients could attain the HbA1c levels below 7% with monotherapy, and by 9 years, this declined to approximately 25% [70]. Compared with OADs, intensive insulin therapy causes rapid improvement in β cell functions of treatment-naïve T2DM patients, thereby helping maintain long-term normoglycemia, thus supporting the rationale for early initiation of insulin in T2DM.

Current ADA guidelines recommend early introduction of insulin if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (> 10% [86 mmol/mol]) or blood glucose levels (≥ 300 mg/dL [16.7 mmol/L]) are very high [28]. The 6-year-long Outcome Reduction with Initial Glargine Intervention (ORIGIN) study has reported a stable pattern of glycemic control while other studies have reported the beneficial effects on β cell functions in patients with T2DM who were on early insulin therapy in combination with OADs [71–73]. In 2018, a prospective observational study by Mokta et al. looking at use of insulin therapy in symptomatic newly diagnosed T2DM Indian adults (HbA1c > 9%) reported a significant improvement in fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), and A1C as well as β cell function after 8 weeks of therapy [74]. Another recent Indian study by Madnani et al. also reported long-term good glycemic control and improved beta functions (which is sustained up to 2 years) after short-term insulin therapy (4–6 weeks) in treatment-naïve patients with type 2 diabetes [75].

To date, no studies have examined the comparative effectiveness of the stepwise addition of insulin therapy over time versus early therapy in combination with OADs.

Total daily dose of insulin

The insulin dose must be individualized for each patient based on the blood glucose profile and clinical setting. The starting dose of basal insulin should be 0.1–0.2 units/kg/day or 10 U [76]. It is better to start with small doses and modify accordingly every 3 days. The dosage depends on many factors such as [77, 78]

- Age
- Weight
- Stage of puberty
- Duration and phase of diabetes
- State of injection sites
- Nutritional intake and distribution
- Exercise patterns
- Daily routine
- Blood glucose levels and glycated hemoglobin
- Intercurrent illness

Initiation insulin algorithm for patients with T2DM

The current ADA guidelines strongly advocate a "patient-centered approach" to the treatment of T2DM and suggest that the individualization of treatment is the "cornerstone of success." A diabetic meal plan matches calories from foods (carbohydrates, proteins, and fats or oils) to individual body activity and insulin levels. This approach should focus on matching the supply of insulin to the regular exercise/diet patterns of patients and follow-up with regular SMBG [28, 79].

Once a clinical decision has been made to initiate insulin therapy in patients with T2DM based on several indications described above, ADA 2019 guidelines recommend initiating

Table 4 Summary of clinical evidences for non-insulin regimens in management of T1DM

Author	Design/population	Objectives	Regimens	Results
Riddle, 2018	A randomized, two-way crossover study	Amylin analog pramlintide and insulin vs. placebo and insulin	Regular human insulin was delivered with pramlintide or placebo using separate infusion pumps in a fixed ratio (9 μg/unit) over a 24-h period	• Compared with placebo, pramlintide showed reduction in - Mean 24-h glucose (8.5 vs. 9.7 mmol/L; $p = 0.012$) - Glycemic variability - Postprandial glucagon - Triglycerides
Galderisi, 2018	Two parallel studies were conducted	Pramlintide vs. liraglutide	Participants underwent mixed-meal tolerance tests (MMTTs) before and after 3 to 4 weeks of treatment with either pramlintide ($n = 8$) or liraglutide ($n = 10$)	• Compared with baseline, - Pramlintide reduced the peak increment in glucagon from 32 ± 16 to 23 ± 12 pg/mL ($p < 0.02$) - Liraglutide had no effect on plasma glucagon
GLP-1 agonist				
Mathieu, 2016	A 52-week, double-blind, treat-to-target trial	Liraglutide added to treat-to-target insulin	1398 adults (3:1) received once-daily SC injections of liraglutide (1.8, 1.2, or 0.6 mg) or placebo added to insulin	• Liraglutide added to treat-to-target - Insulin reduced - HbA1c levels, - Total insulin dose, - Body weight • However, it was accompanied by increased rates of - Symptomatic hypoglycemia - Hyperglycemia with ketosis
Frandsen, 2017	A 12-week randomized, placebo-controlled, double-blind, parallel-group study	Evaluate of liraglutide on counter-regulatory responses and GE rate during hypoglycemia	20 patients (1:1) received liraglutide 1.2 mg once daily or placebo as add-on to insulin treatment	• No difference between groups in - GE rates ($p = 0.96$), - Glycemic recovery, - Counter-regulatory hormone responses, - Systolic blood pressure, - GLP-1 responses, and - PP responses • Liraglutide increased heart rate from 69 ± 4 to 80 ± 5 beats/min ($p = 0.02$)
Dube et al., 2018	A crossover, double-blinded, 24-week intervention study	Liraglutide added to basal/bolus insulin	15 participants (1:1) received placebo or liraglutide for 24 weeks including a 1-month titration period from 0.6 to 1.2 to 1.8 mg, in addition to their insulin	Liraglutide + basal/bolus insulin improved the anthropometric and metabolic profiles without an increase in hypoglycemia
Metformin				
Anderson, 2017	12-month double-blind RCT	Metformin vs. placebo	Metformin (up to 1 g twice a day) or placebo in children	• Metformin - Improved glyceryl trinitrate mediated dilatation by 3.3 percentage units ($p = 0.03$) - HbA1c at 3 months ($p = 0.001$) - Reduced insulin dose by 0.2 U/kg/day (95% CI 0.1, 0.3, $p = 0.001$)

basal insulin in patients with T2DM [28]. Recent RSSDI guidelines recommend to initiate insulin in patients with T2DM with once-daily basal insulin, once-daily premixed/co-formulation insulin, or twice-daily premixed insulin, either alone or in combination with other OADs, or initiate a combination of basal insulin and GLP1RA, based upon patient's age, clinical features, glucose profile, risk of hypoglycemia, and patient preference [80]. The International Diabetes Federation (IDF) guidelines recommend initiation of insulin therapy with either basal or premix insulins [81]. Indian Consensus on Initiation and Intensification of Premix Insulin recommends premix insulin analogs over human premix insulins because of the lower incidence of severe hypoglycemia, less nocturnal hypoglycemia, and flexibility of administration [82]. Initiation with only premix insulin is recommended by The Indian National Consensus Group (INCG) 2013. Also, the INCG recommends initiation of insulin in newly diagnosed T2DM patients as rescue therapy [83]. A practical algorithm for insulin initiation and intensification in T2DM is shown in Fig. 9.

Insulin regimens for T2DM

Basal insulin regimen

Basal insulin alone or in combination with metformin and other OADs is the most convenient initial insulin regimen. Basal insulin is initiated at 10 U or 0.1–0.2 U/kg/day and then up-titrated based on the FPG value. However, in patients with more severe hyperglycemia, the starting dose can be 0.3–0.4 units/kg/day with individualized titration over days to weeks as needed. Steps for initiating basal insulin in patients with T2DM are shown in Table 5. The principal action of basal insulin is to restrain hepatic glucose production and to maintain euglycemia overnight as well as between meals. Fasting glucose levels can be controlled with either human NPH insulin or long-acting insulin analogs. In clinical trials, U-100 glargine or detemir has shown less risk of symptomatic and nocturnal hypoglycemia compared with NPH insulin [84, 85]. However, other studies involving U-300 glargine or degludec suggest a lower hypoglycemia risk compared with U-100 glargine plus OADs [86, 87]. Despite evidence for lower hypoglycemia risk with newer, longer-acting basal insulin analogs, human insulin (NPH) may be the appropriate choice for many patients with T2DM (e.g., individuals with low rates of hypoglycemia, relaxed A1C goals, and prominent insulin resistance, as well as those with cost concerns).

Bolus-only insulin regimen

In 2011, a meta-analysis involving 16 randomized controlled trials and 7759 T2DM patients found a higher rate of achieving the HbA1c target with biphasic or prandial insulin compared with basal insulin [88]. The onset 2 trial which compared fast-acting insulin aspart (faster aspart) and insulin aspart (IAsp) in inadequately controlled T2DM patients reported confirmed noninferiority in reducing HbA1c and change from baseline in HbA1c. Both faster aspart and IAsp improved PPG level; though, the PPG increment was statistically significant in favor of faster aspart after 1 h ($p = 0.0198$), but not after 2–4 h. No difference between groups was reported regarding the change from baseline in fasting plasma glucose, overall severe hypoglycemia rates, and body weight (rate ratio [RR] [95% CI] 1.09 [0.88; 1.36]) [89].

Premix insulin regimen

Premixed insulins are fixed component formulations of rapid-acting and intermediate- or long-acting insulins for both fasting and postprandial glycemic control. Premixed insulin contains both a basal and prandial component (NPH/regular 70/30, 70/30 aspart mix, 75/25, or 50/50 lispro mix), which facilitates insulin requirement of both basal and prandial phase in a single injection. Steps for initiating premixed insulin in

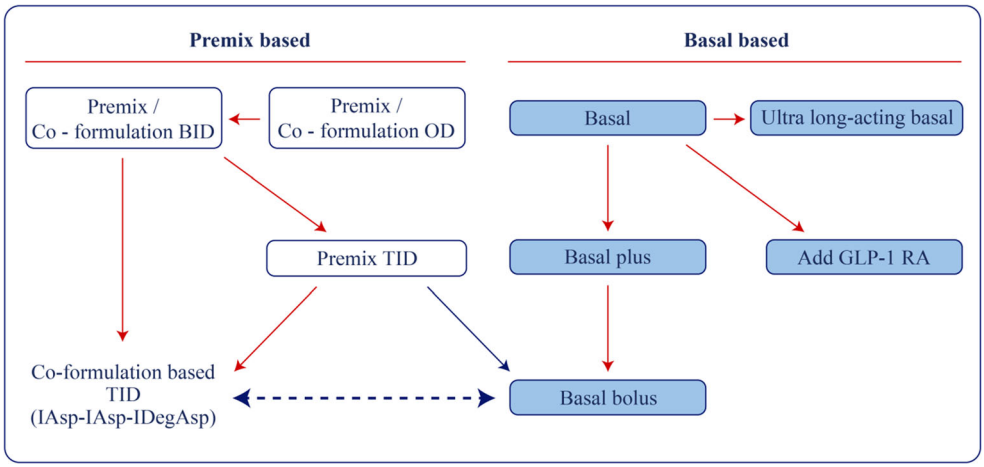

Fig. 9 Practical algorithm of insulin regimens for insulin initiation and intensification. OD, once daily; BID, twice daily; TID, three times a day; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IAsp, insulin aspart; IDegAsp, mix of insulin degludec and insulin aspart. Adapted from RSSDI clinical practice recommendations for the management of type 2 diabetes mellitus 2017 [80]

Table 5 Steps for initiating basal insulin

	Glucose value	Total daily dose
Step 1. Initiation with basal insulin*	A1C < 8%	0.1–0.2 U/kg
	A1C > 8%	0.2–0.3 U/kg
Step 2. Titration#	Fixed regimen	Increase by 2 U/day
(every 2–3 days to reach glycemic goals)	Adjustable regimen	
	FPG > 180 mg/dL	Add 4 U
	FPG 140–180 mg/dL	Add 2 U
	FPG 110–139 mg/dL	Add 1 U
Step 3. Monitor for hypoglycemia	BG < 80 mg/dL	Reduce by 10 to 20%
	BG < 56 mg/dL	Reduce by 20 to 40%

Adapted from RSSDI clinical practice recommendations for the management of type 2 diabetes mellitus 2017 [80]

A1C glycated hemoglobin, *BG* blood glucose, *FPG* fasting plasma glucose, *NPH* Neutral Protamine Hagedorn, *SU* sulfonylureas

* Consider discontinuing SU therapy and basal analogues should be preferred over NPH insulin

For most patients with T2D taking insulin, glucose goals are A1C < 7% and fasting and premeal blood glucose < 110 mg/dL in the absence of hypoglycemia. A1C and FPG targets may be adjusted based on patients age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

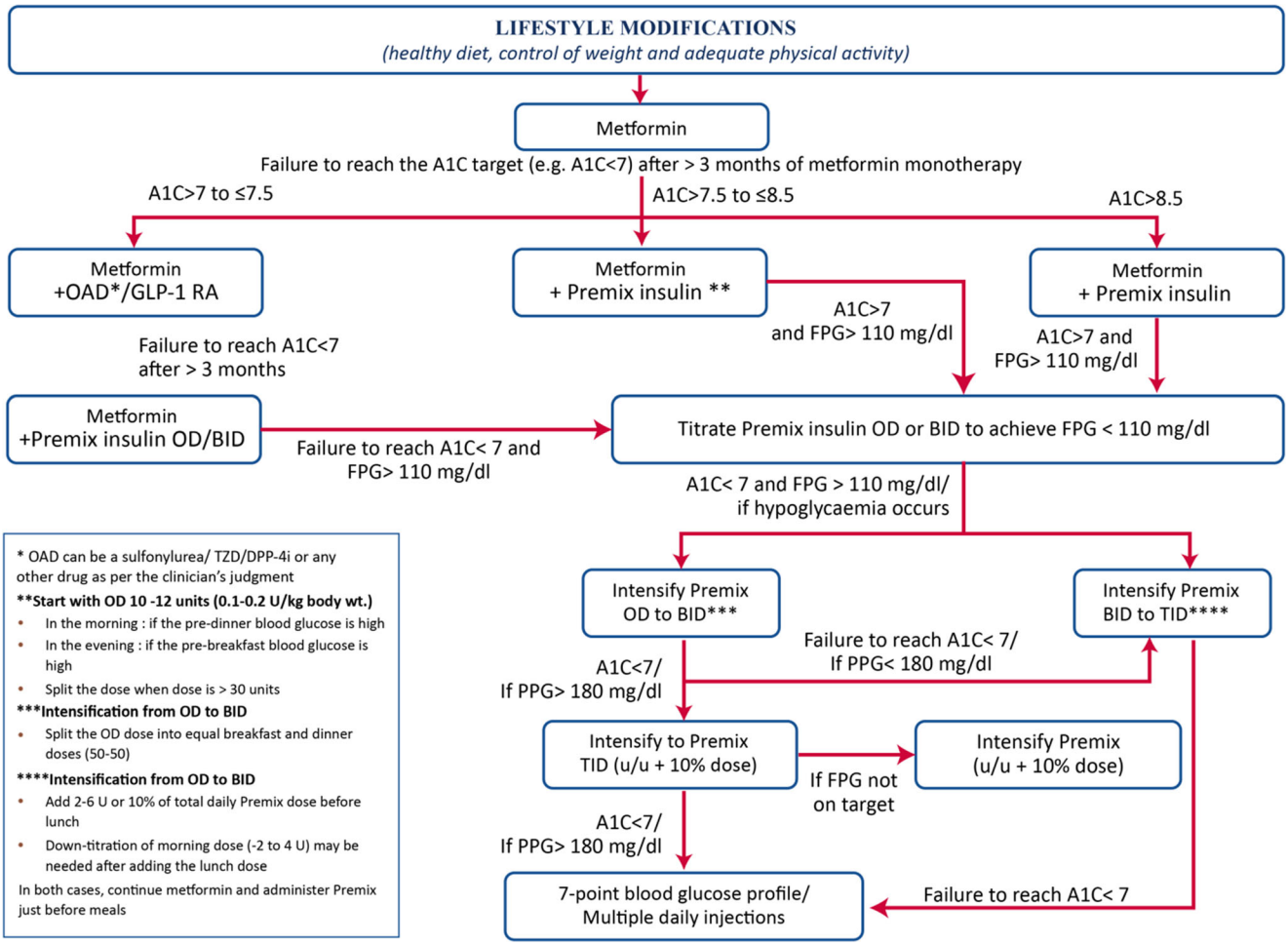

Fig. 10 Steps for initiating premixed insulin. OAD, oral antidiabetic agents; GLP-1 RA, glucagon-like peptide-1 receptor agonist; OD, once daily; BID, twice daily; TID, three times in a day; TZD, thiazolidinedione; DPP-4I, dipeptidyl peptidase-4 inhibitors; FPG, fasting plasma glucose; PPG, postprandial plasma glucose. Adapted from RSSDI clinical practice recommendations for the management of type 2 diabetes mellitus 2017 [80].

patients with T2DM are shown in Fig. 10. The 4-T study compared the efficacy and safety of three analog insulin regimens in T2DM patients inadequately controlled on sulfonylurea-based treatment regimen. Patients with HbA1C ranging between 7 and 10% were randomly assigned to receive biphasic insulin aspart twice daily, prandial insulin aspart thrice daily, or basal insulin detemir once daily. A comparable reduction in HbA1C was observed after 3 years; however, the basal regimen resulted in fewer hypoglycemic episodes and less rapid weight gain than other insulin regimens [90, 91]. A systematic review of 28 randomized controlled trials (N = 30,588) evaluated the effectiveness of insulin analogs to reach the HA1c target of < 7% in T2DM patients. As compared with basal insulin, a higher proportion of patients treated with BIAsp 30 achieved the glycemic target (46.5% vs. 41.4%) [88]. In 2013, a 24-week treatment to target trial that included Chinese and Japanese insulin-naïve subjects with T2DM showed similar HbA1c reduction and safety profile with both once-daily biphasic insulin aspart 30 (BIAsp 30) and once-daily insulin glargine [92]. Similar findings were also reported by another open-label, randomized GALAPAGOS study comparing insulin glargine (± glulisine) strategy and a premixed insulin strategy which showed similar percentages of well-controlled patients without hypoglycemia [93].

Combination of oral hypoglycemic agents with insulin

Weight gain and increased episodes of hypoglycemia preclude the use of exclusively insulin-based regimes in poorly controlled T2DM patients [94]. In 2019, a systematic review, network meta-analysis, and cost-effectiveness analysis evaluating the comparative efficacy and safety of lixisenatide combined with basal insulin versus intensive premix insulin (premix) in patients with T2DM inadequately controlled by basal insulin reported similar HbA1c reduction compared with premix insulin, accompanied by lower risk of hypoglycemia and greater body weight reduction [95]. Recently, Castellana et al. conducted a systematic review and meta-analysis to compare the effects of GLP-1RA/insulin combinations versus BP/BB. Compared with BP/BB, GLP-1RA/insulin combinations were associated with a similar HbA1c reduction ($\Delta = -0.06\%$; 95% confidence interval [CI], −0.14 to 0.02; $p = 0.13$; $I^2 = 52\%$), greater weight loss ($\Delta = -3.72$ kg; 95% CI, −4.49 to −2.95; $p < 0.001$; $I^2 = 89\%$), and lower incidence of hypoglycemic events (relative risk [RR] = 0.46; 95% CI, 0.38 to 0.55; $p < 0.001$; $I^2 = 99\%$). The daily insulin dosage among GLP-1RA/insulin users was 30.3 IU/day (95% CI, −41.2 to −19.3; $p < 0.001$; $I^2 = 94\%$), lower than with BP/BB. No difference was found for discontinuation due to lack of efficacy [96]. In 2011, a meta-analysis involving 11 prospective randomized controlled trials and 2171 adults with uncontrolled T2DM reported significant efficacy/safety benefits following the addition of insulin glargine to metformin monotherapy at an earlier treatment stage over regimens including SU [97]. In 2014, a Korean study reported a significant improvement in overall glycemic control with combination therapy of metformin and glimepiride plus glargine insulin compared with the other combinations. However, risk of hypoglycemia and the weight gain did not significantly differ among the treatment groups [98].

The Prospective Pioglitazone Clinical Trial in Macrovascular Events study (PROactive) evaluated the use of pioglitazone in combination with insulin treatment. A lasting improvement in glycemic control with a rapid and sustained decrease in insulin doses was observed as compared with the placebo group [99]. More patients with poorly controlled T2DM despite high doses of insulin in the pioglitazone plus insulin group showed the maximum reduction in HbA1C. In 2009, a systematic review and meta-analysis involving eight randomized controlled trials comparing pioglitazone as an add-on therapy to insulin and the same insulin regimen reported small advantage of HbA1c reductions following the addition of pioglitazone but at the cost of weight gain and increased hypoglycemia [78]. Add-on therapy of sodium-glucose cotransporter-2 inhibitor (SGLT2i) and dipeptidyl peptidase 4 (DPP4) inhibitors with insulin reported a significant improvement in glycemic control as compared to insulin alone without increasing hypoglycemia events [100, 101].

In 2016, a meta-analysis by Min et al. comparing SGLT2i inhibitors and DPP4 inhibitors added to insulin therapy in T2DM patients (14 randomized controlled trials comprising 6980 patients) reported better glycemic control and greater weight reduction with SGLT-2 inhibitors. Metformin should be continued in those patients who started on insulin therapy, while other OADs may be continued or discontinued on an individual basis [102].

Recommendations from RSSDI for insulin initiation in patients with T2DM

- "Providers should avoid using insulin as a threat or describing it as a sign of personal failure or punishment."
- As newer and effective OADs have been made available, it is recommended to consider insulin in cases where patient fails to achieve or maintain A1C levels after administration of three OADs; out of which one should be a newer agent or if patient is intolerant to any individual agent or combination of agents.
- Though there are several new oral agents available, their glucose-lowering potential is relatively less when compared with insulin and hence, insulin should never be delayed if A1c remains high.
- When there is evidence of glucose toxicity and lipotoxicity and if the HbA1c is more than 10% at the time of diagnosis, a short course of insulin for about a month can be considered.
- Involvement of patient and physician is important in making a decision regarding the therapeutic choice of regimen, preparation, and delivery device.
- The initial regimen of insulin therapy based upon patient's age, clinical features, glucose profile, risk of hypoglycemia, and patient preference includes OD basal insulin, premixed/co-formulation insulin, or BID premixed insulin, either alone or in combination with

other OADs. Also, basal insulin, either alone or in combination with GLP-1 analogs in same pen device can be used.

▪ Individuals suffering from severe hyperglycemia and life-threatening or organ/limb-threatening clinical situations will require basal-bolus insulin regimens.

▪ Analog insulins may be preferred over human insulins as they possibly lower the risk of nocturnal and symptomatic hypoglycemia; however, economic considerations must be taken into account.

– Timing of insulin and meals should be matched.

– Patients who are initiating insulin therapy should be educated about SMBG and preventive measures regarding hypoglycemia.

▪ Guidance should be provided regarding dose adjustments, administration, storage, and other practical aspects of insulin.

Titration for insulin therapy in T2DM

ADA 2019 guidelines recommend initiation of basal insulin at 10 U or 0.1–0.2 U/kg/day depending on the degree of hyperglycemia. This guideline also suggests an evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach the target fasting blood glucose (FBG) without hypoglycemia. The recommended target for FPG level is 80–130 mg/dL, and PPG level is < 180 mg/dL. These targets can be individualized based on the risk of hypoglycemia and the urgency for glycemic control. Guidelines also suggest titration to be done at regular and short intervals to attain glycemic goals without causing hypoglycemia [28]. The CID 2015 Expert Recommendation suggests titrating the dose of premix and prandial insulin once in a week. This titration should be based on pre-dinner or pre-breakfast values for premix insulin and 2-h post-meal value for prandial insulin, respectively. The starting dose for prandial insulin is 4 U or 10% of basal dose. Both ADA and CID recommendations suggest reducing the dose by 10–20% in the case of hypoglycemia [76]. Summary of published evidence from several clinical trials, which evaluated basal insulins (NPH, IGlar, Insulin Detemir, or IDeg) using different titration algorithms, is provided in Table 6 [103–106].

Steps for dosing and titration in patients with T2DM are shown in Fig. 11.

Recommendations from RSSDI for insulin titration in patients with T2DM

- Insulin regimen should be initiated as defined in the algorithm, using a self-titration regimen and increasing the dose by 2–4 U every 3 days or biweekly or with more frequent contact with a healthcare professional.
- Pre-meal glucose levels and PPG levels should be aimed between 80 and 130 mg/dL and between 140 and 180 mg/dL respectively. These targets can be individualized, based upon the risk of hypoglycemia and the urgency for glycemic control.
- Titration should be performed at regular and short intervals, as guided by the physician or trained paramedical staff to achieve glycemic goals without causing hypoglycemia.
- Initially titration should be done to control fasting blood sugar level, followed by post-meal value for prandial insulin with the highest glycemic excursion in sequential order.

Intensification for insulin therapy in T2DM

Intensification of insulin therapy is recommended when patients fail to achieve glycemic goals even after optimal dose titration. As per the 2013 INCG recommendations, intensification of premix insulin to twice and thrice daily is required if HbA1c is > 7.0% (> 53 mmol/mol) and FPG is > 6.1 mmol/L [83]. In cases where suboptimal glycemic control with premix/basal insulin is observed, then, twice-daily insulin degludec/insulin aspart 70/30 (co-formulation) is preferred for intensification. As per the findings of a recently conducted systematic review, insulin degludec/insulin aspart 70/30 twice daily is comparable with biphasic insulin aspart 30 twice daily in T2DM patients requiring insulin-based treatment. This also resulted in a lower risk of nocturnal hypoglycemia [107]. An improved long-term glycemic control with a greater reduction in fasting glucose at a reduced dose and less nocturnal hypoglycemia was observed with insulin degludec/insulin aspart 70/30 as compared with biphasic insulin aspart 30 [108–110]. Steps for intensification of insulin therapy in patients with T2DM are shown in Table 7.

Recommendations from RSSDI for insulin intensification in patients with T2DM

▪ Insulin therapy should be intensified in case patients fail to achieve glycemic goals even after optimal dose titration.

▪ Options to be considered during intensification:

– Prandial insulin can be added to basal insulin (basal plus or basal-bolus), starting with largest meal of the day

– Premix insulin should be administered twice daily or thrice daily (rarely)

– Insulin co-formulation-based regimen can be followed

– Addition of GLP-1 analogs

o Intensification strategy can be based upon various factors such as dietary pattern, lifestyle, risk of hypoglycemia and weight gain, affordability, and patient preference.

- Basal plus regimen is a stepwise approach used for insulin intensification, leading to basal-bolus prescription. It is associated with lesser risk of hypoglycemia and weight gain than basal-bolus regimen.
- Both premix insulin therapy and co-formulation insulins are acceptable methods of intensification; however, co-formulation insulin offers lower risk of hypoglycemia and nocturnal hypoglycemia. These preparations are also free of resuspension errors.

Diabetes in pregnancy

A steady increase in the prevalence of diabetes in pregnancy has been witnessed in the past few years, especially in developing countries like India. Gestational diabetes mellitus (GDM) is the main cause of diabetes seen in pregnancy while the remaining cases are of preexisting T1DM and T2DM. As compared with women from other parts of the world, it is observed that Indian women have 11 times more risk of developing GDM. The prevalence of GDM in India varies in different regions with a reported prevalence of 3.8% in

Kashmir, 9.5% in Western India, 6.2% in Mysore, and 22% in Tamil Nadu [111].

Glycemic targets in pregnancy

Ideally, the A1C target in pregnancy is 6% (42 mmol/mol) if this can be achieved without significant hypoglycemia, but the target may be relaxed to 7% (53 mmol/mol) if necessary to prevent hypoglycemia [112].

Insulin in women with GDM

Indian consensus evidence-based guidelines 2014 recommend insulin initiation if nutrition therapy or meal plan fails to achieve blood glucose targets within 2 weeks of their initiation in women with GDM [113]. The ADA guideline 2019 recommends insulin initiation along with lifestyle change in women with GDM if needed to achieve glycemic targets. The ADA guideline 2019 also stated that insulin is the "preferred medication for treating hyperglycemia in GDM," as it does not cross the placenta to a measurable extent. Metformin and glyburide should not be used as first-line agents, as both cross the placenta to the fetus. All oral agents lack long-term safety data [112]. Both insulin aspart and insulin lispro have been found to be safe and efficacious for pre-meal use during pregnancy [114, 115]. In 2007, a randomized trial comparing insulin aspart and regular human insulin in pregnant women with T1DM reported benefits of insulin aspart over human insulin in terms of glycemic control (difference in PPG − 0.40%, $p = 0.044$) and lower hypoglycemia events (major hypoglycemia, 1.4 vs. 2.1 episodes/year exposure) [116]. Another study comparing insulin analog (insulin aspart and regular human insulin) with no insulin in GDM reported higher peak insulin concentration and lower peak glucose and C-peptide concentrations with both insulin preparations than with no exogenous insulin. However, glucose areas under the curve above baseline were significantly lower with insulin aspart (180-min area, 7.1 mg h dL^{-1}; $p = 0.018$), but not with regular insulin (30.2 mg h dL^{-1}; $p = 0.997$), than with no insulin (29.4 mg h dL^{-1}) [115]. Basal insulin therapy for GDM may continue to focus on NPH insulin along with insulin detemir, which has been approved for use during pregnancy. In a randomized, controlled noninferiority trial ($n = 310$), treatment of T1DM pregnant women with insulin detemir resulted in lower FPG and noninferior HbA1c compared with NPH insulin; FPG was lower for insulin detemir versus NPH (85.7 vs. 97.4 mg/dL, $p = 0.017$), while the estimated HbA1c at 36 gestational weeks was 6.27% for insulin detemir and 6.33% for NPH [117]. Randomized trial evidence suggests insulin detemir is noninferior to insulin NPH for the treatment of GDM and T2DM in pregnancy. More hypoglycemic events per patient were noticed in the NPH group [118]. In 2017, a Cochrane review (included 53 relevant studies and 7381 women) evaluating the effects of insulin in treating women with GDM reported similar effects of insulin and OADs on the risk of preeclampsia (RR 1.14, 95% CI 0.86 to 1.52), the risk of birth by cesarean section (RR 1.03, 95% CI 0.93 to 1.14), or the risk of developing T2DM (metformin only) (RR 1.39, 95% CI 0.80 to 2.44). The choice to use insulin or oral antidiabetic agents may be down to physician or maternal preference, availability, or severity of GDM [119].

Recommendations from RSSDI for insulin therapy in women with GDM

- Pharmacological therapy should be initiated in women with GDM if they fail to achieve blood glucose targets within 2 weeks of initiation of nutritional therapy and exercise.
- As insulin does not cross the placenta, it is the preferred agent in women with GDM.
- Insulin aspart/lispro may be preferred over human insulin for better postprandial control.
- NPH or insulin detemir can be used for basal insulin requirements.

Insulin in pregnant women with preexisting T1DM and T2DM

The ADA guideline 2019 on the management of preexisting T1DM and T2DM in pregnancy recommends insulin as the preferred agent because it does not cross the placenta and because oral agents are ineffective in T1DM and are generally insufficient to overcome the insulin resistance in T2DM [112]. A meta-analysis assessing the efficacy and safety of three available rapid-acting insulin analogs (insulins lispro, aspart, and glulisine, respectively) in pregnant women with T1DM or GDM found insulin lispro and insulin aspart as safe and effective approach for both mother and fetus, with glycemic control at least as good as with regular human insulin (RHI). There were no data on insulin glulisine during pregnancy [120]. Glargine and detemir have primarily been assessed in women with preexisting diabetes in pregnancy. According to the results of a randomized control trial, IDet is safe and may afford less maternal hypoglycemia compared with NPH, while observational studies suggest that glargine, although theoretically less desirable, is also safe [121]. A recent Cochrane systematic review was not able to recommend any specific insulin regimen over another for the treatment of diabetes in pregnancy [122]. Another systematic review evaluating CSII versus MDI in T1DM-complicated pregnancy showed a lower HbA1c level with CSII versus MDI in the first trimester (WMD − 0.45%; 95% CI − 0.62, − 0.27); however, this difference decreased in subsequent trimesters. CSII therapy was associated with lower insulin requirements and higher gestational weight gain, and

was more likely to be large for gestational age and less likely to be small for gestational age [123].

Recommendations from RSSDI for insulin therapy in pregnant women with preexisting T1DM and T2DM

- Insulin is considered more suitable over oral agents in women with preexisting diabetes as they are unable to overcome the insulin resistance in T2DM as well as cross the placenta, and are ineffective in T1DM.
- An individualized insulin regimen and glycemic targets by basal-bolus injection therapy should be provided to every individual pregnant woman with preexisting diabetes.
- Regular insulin or rapid-acting analogs may be used in women with preexisting diabetes to improve postprandial blood glucose.
- Detemir or glargine may be used in women with preexisting diabetes as an alternative to NPH and is associated with similar perinatal outcomes.
- Women with T1DM and insulin-treated T2DM who receive antenatal corticosteroids to improve fetal lung maturation should follow a protocol that increases insulin doses proactively to prevent hyperglycemia.

Insulin dosing in pregnancy

Insulin has long been considered the standard of care to attain optimal glucose control in pregnancy, although multiple methods are available to initiate insulin. Weight-based dosing, weight plus gestational age-based dosing, and even a "one-dose-for-all" type of dosing have been used (Fig. 12) [124].

The CDAPP Sweet Success program offers some guidance on adjustments, suggesting changes by 2–4 units (~ 10%) in short- and intermediate-acting insulins every 2–3 days. Women with GDM or T2DM rarely have hypoglycemia unawareness. Therefore, the most aggressive adjustments can safely be made in this population. In practice, adjustments can be made every couple of days until control is attained if personnel and time allow [124].

In the case of aggressive titration, it is difficult to adjust the dose of new long-acting insulin analogs as rapidly as with NPH. Insulin detemir can be safely titrated every 3 days by 3 units in non-pregnant patients. However, insulin glargine U-100 has two suggested options for dosing adjustments in non-pregnant patients: either by 1 unit every day or by 2 units every 3 days. Insulin glargine U-300 should only be adjusted every 3–4 days [124].

Monitoring during pregnancy

Frequent SMBG is essential to guide the therapy of GDM. To improve fetal outcomes, both fasting and postprandial testing are recommended. In the recently published revised guidelines on diagnosis and management

Table 6 Summary of published evidence for dosing and titration

Author and study population	Target and SMPG value	Starting dose	Titration algorithm followed
Kennedy et al. 2006 *N* = 7893	FPG ≤ 100 mg/dL Titration based on mean FPG (mg/dL) over previous 2–4 days	Insulin glargine, 10 U/day	• 100–119 → + 0–2 U • 120–139 → + 2 U • 140–159 → + 4 U • 160–179 → + 6 U • ≥ 180 → + 8 U • < 70 → dose reduced to previous level Severe hypoglycemia → stop upward titration for 1 week
Meneghini et al. 2007 *N* = 5604	FPG 80–110 mg/dL Titration based on mean FPG (mg/dL) over previous 3 days	Insulin Detemir: 0.32–0.34 U/kg	• < 80 → − 3 U • 80–110 → no change • > 110 → + 3 U
Franek et al. 2015 *N* = 394	FPG 70–90 mg/dL Titration based on mean FPG (mg/dL) over previous 3 days	IDegAsp: 06 U/twice daily	• < 56 → − 4 U (if dose > 45 units, reduced by 10%) • ≤ 70 → − 2 U (if dose > 45 units, reduced by 5%) • ≤ 90 → no change • < 126 → + 2 U • < 144 → + 4 U • < 162 → + 6 U • ≥ 162 → + 8 U
Fahrbachet al. 2008 *N* = 2000	FPG 80–109 mg/dL Titration based on mean FPG (mg/dL) over previous 3–7 days	Lispro: 10 U/twice daily	• < 80 → − 2 U • 80–109 → no change • 110–139 → + 2 U • 140–179 → + 4 U • ≥ 180 → + 6 U

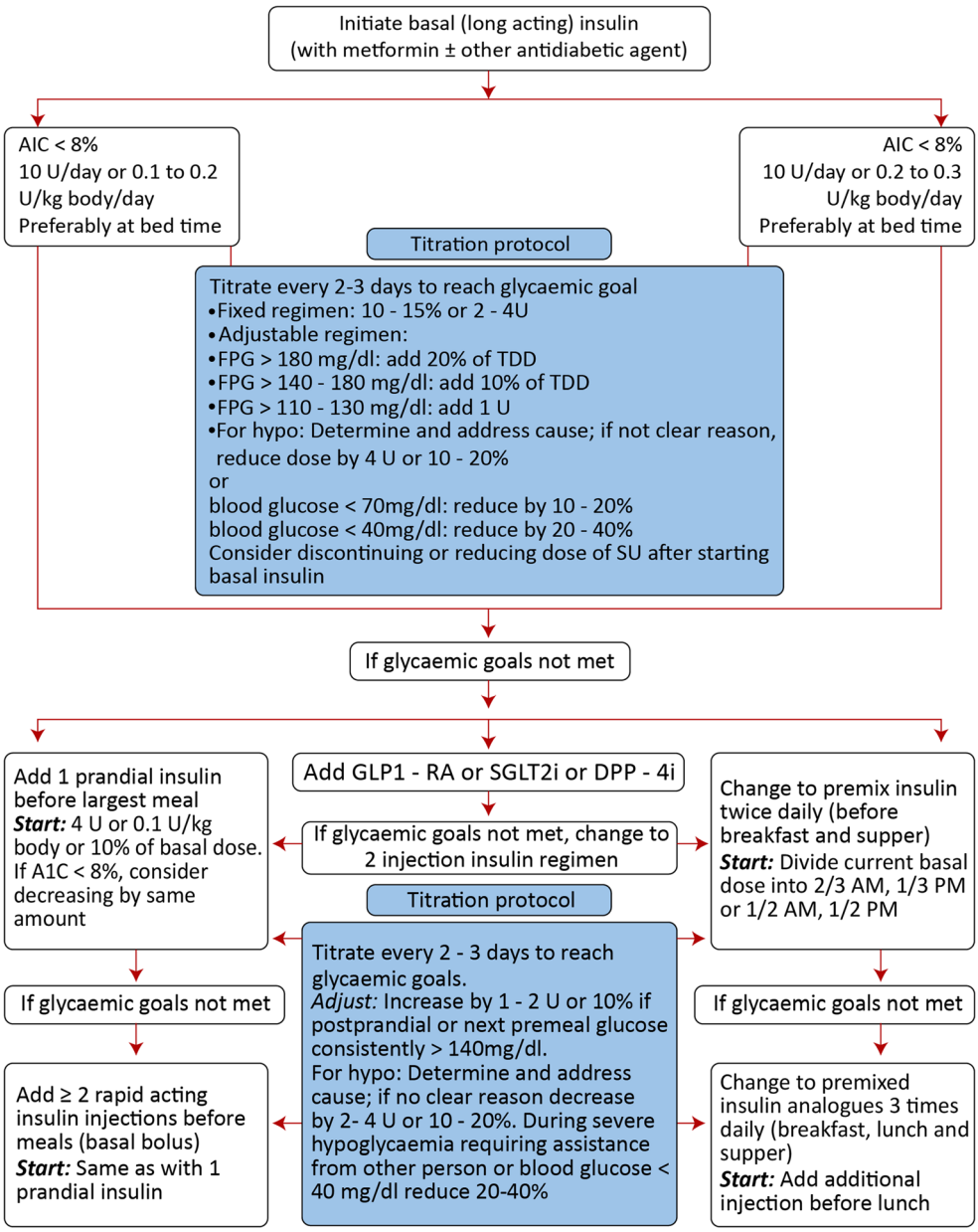

Fig. 11 Algorithm for insulin titration in T2DM. TDD, total daily dose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitors; DPP-4i, dipeptidyl peptidase-4 inhibitors. Adapted from RSSDI clinical practice recommendations for the management of type 2 diabetes mellitus 2017 [80].

of GDM, the Government of India has recommended target FBG and 2-h postprandial levels as less than 95 mg/dL and 120 mg/dL respectively [125]. A study has shown that women with preexisting T2DM from central India have a significantly higher post-dinner blood glucose than post breakfast. Therefore, women on insulin-based regimens should do frequent testing including fasting, 2-h post breakfast, 2-h post-lunch, and 2-h post-dinner for insulin dose adjustment [125]. The IDF guidelines also advise women with GDM to perform SMBG four times daily (fasting and 1 h after each meal) [126]. In 2019, a prospective study comparing OGTT and SMBG in 103 pregnant women reported improvement in the care of pregnant women with SMBG [127]. According to recently completed randomized controlled trials, CGM is beneficial in the management of GDM. In a prospective cohort study, 340 Chinese pregnant women were allocated to either the CGM group (n = 150) or the routine care group (n = 190). Women using CGM had fewer BG values out of the target range, less glucose variability, and less primary cesarean section preeclampsia and lower infant birth weight [128]. Another randomized controlled trial comparing antenatal care plus CGMS and SMBG in 106 women with GDM reported a significant reduction in gestational weight gain with antenatal care plus CGMS (especially with early CGMS) compared with women doing only SMBG [129]. A1C was lower in the CGM group but not statistically significantly different. Compared with intermittent glucose monitoring, CGM may reduce hypertensive disorders of

pregnancy. However, this did not translate into a clear reduction for preeclampsia, and so this result should be viewed with caution [130].

Recommendations from RSSDI for SMBG during pregnancy

- Ideal SMBG is seven tests/day, i.e., three before and three after each respective meal and one test at 3 AM. If this is not practicable, other approach should be encouraged which includes one fasting test and three tests each 1 h after breakfast, lunch, and dinner daily may be done, which can further be individualized to twice or thrice a week as the pregnancy advances.

Monitoring of blood glucose

Both ADA 2019 guideline and RSSDI 2018 consensus recommend glucose level assessment before meals and exercise, at bedtime, and occasionally postprandially in most diabetic patients on intensive insulin regimens (MDI or insulin pump therapy) using SMBG or a CGM [80, 131]. Although individual blood glucose monitoring needs vary, many patients using insulin regimens will require monitoring up to 6–10 times daily. A database study of 26,723 children and adolescents aged 0–18 years with T1DM showed that, after adjustment for multiple confounders, increased frequency of SMBG was significantly associated with better metabolic control (− 0.2% lower A1c per additional test per day) with fewer acute complications [132]. A trial by Young et al. comparing 3 approaches of SMBG (no SMBG, once-daily SMBG, and once-daily SMBG with enhanced patient feedback) reported no significant differences in HbA1c levels and health-related quality of life at 1 year [133]. A meta-analysis by Malanda et al. involving 12 randomized controlled trials and 3259 patients suggested that SMBG can reduce A1c by 0.3% at 6 months; though non-significant SMBG-induced decrease was seen at 12 months (− 0.1; 95% CI − 0.3 to 0.04; 493 participants, two trials) in patients with T2DM who were not using insulin [134]

Table 7 Steps for intensification of insulin therapy

Basal insulin	Prandial insulin	Premixed insulin
• Given preferably before dinner to achieve adequate suppression of HGP • Target: FPG < 120 • Initiate with 10 U at bedtime and check FBSL • Increase dose by 1 U/day or 3 U every 3 days by patient self-titration until target FBSL is achieved	• Initiate along with meal with highest glycemic excursion • Start with 4 U and increase by 1 U/day or 3 U/3 days till PPBG < 180 • Next meal with highest glycemic excursion should be titrated similarly • Full basal-bolus can be considered for effective prandial control after all meals	• Calculate the total dose • Start with 6 U BID day for analogs and 2/3rd dose in morning and 1/3rd dose in evening for human insulins • Titration can be done for morning dose based on pre-dinner values and for evening dose based on FBG • Titration can be done by 1 U/day or 3 U/day to achieve required BG targets

Adapted from Bajaj S. RSSDI clinical practice recommendations for the management of type 2 diabetes mellitus 2017

Recommendations from RSSDI for SMBG

- SMBG should be accessible on an ongoing basis to patients using insulin therapy.
- Regular SMBG is recommended for patients who are on MDI insulin therapy, pre-gestational/GDM on insulin, history of hypoglycemia unawareness, brittle diabetes, or with poor metabolic control on multiple oral antidiabetic agents (OADs) and/or basal insulin.
- Patients on intensive insulin regimens who are on multiple doses of insulin or on insulin pumps should be tested three or more times daily (all pre-meals, post-meals, bedtime, prior to exercise).

Insulin therapy during lactation

Indian National Consensus Group 2012 recommended dose adjustment of premixed insulin in lactating mothers on an individual basis while National Danish guidelines recommend an individualized diabetes diet for breastfeeding mothers. The Institute of Medicine recommended minimum daily intake for carbohydrate of 210 g per day for lactating mothers to prevent ketonemia. It also recommended carbohydrate counting at all meals and snacks (main sources) [135]. A study by Gunderson et al. showed that lactation may exert favorable effects on glucose metabolism and insulin sensitivity [136]. In a retrospective study from Japan, high-intensity breastfeeding (≥ 6 months) exerted a protective effect against developing abnormal glucose tolerance during the first year postpartum through improving insulin resistance [137]. Another study by McManus et al. demonstrated that 3 months of breastfeeding in women with previous GDM improved pancreatic β cell function; though, no significant difference was found for fasting glucose or insulin values [138].

Recommendations from RSSDI for insulin therapy during lactation

- An individualized diabetes diet for breastfeeding mothers should be encouraged.
- Early neonatal feeding as well as high-intensity breastfeeding should be encouraged in women with preexisting diabetes and GDM.
- Explain to women with insulin-treated preexisting diabetes that they are at increased risk of hypoglycemia in the postnatal period, especially when breastfeeding, and advise them to have a meal or snack available before or during feeds.

Insulin therapy in other special population

Insulin therapy in elderly

In 2011, the South Asian Consensus group recommended that physicians should not avoid usage of insulin in elder patients who often have multiple comorbidities and physical limitations; though, the initiation of insulin therapy is a challenging task in these patients [139]. ADA 2019 guidelines recommend simplification of complex regimens in older adults to reduce the risk of hypoglycemia if it can be achieved within the individualized A1C target. A retrospective observational study of T2DM patients with complications, who were aged 40 years and older, indicated a significant association of age with poor glycemic control [140]. A pilot multicenter study from India depicted that both basal-bolus and premix insulin analogs can be used for initiating insulin therapy in T2DM. However, premix insulin analog showed greater reduction in HbA1C (1.58 vs. 1.16%; $p < 0.05$) as compared with basal-bolus regimen [141]. The DURABLE study post hoc analysis favored premixed analog (biphasic lispro) over basal analog (glargine) in terms of efficacy in lowering HbA1c in older people with T2DM. More hypoglycemic events seen in the premixed arm were attributed to a greater number of their doses and lack of dose titration of concomitant OADs [142]. The findings of the IMPACT India survey reported premix insulin BD as the most preferred regimens for adults (59%) and elderly (53%) [143]. Another prospective, single-center, observational study from India involving 50 elderly confirmed patients of either gender suffering from T2DM reported significantly more hypoglycemia in those receiving insulin. This study also reported that quality of life was not much different in patients using insulin in T2DM [143].

Recommendations from RSSDI for insulin therapy in elderly

- Strategies should be used strictly to prevent hypoglycemia in geriatric patients with diabetes and multiple comorbidities which include the choice of antihyperglycemic therapy and less stringent glycemic goals.
- Deintensification of complex regimens is recommended to lower the risk of hypoglycemia, if it can be achieved within the individualized A1C target.
- Use of premixed insulin and prefilled insulin pens should be encouraged in geriatric population to minimize dosing errors and to potentially improve glycemic control.
- Frequency of hypoglycemic events can be lowered in older people using basal or premix analogs instead of NPH or human 30/70 insulin.
- Overtreatment of diabetes should be avoided in older adults.

Chronic kidney disease

ADA 2019 guidelines does not provide any specific recommendation on the use of insulin in chronic kidney disease (CKD) patients with diabetes; though, the kidney plays an important role in removing the exogenous insulin [144]. Few studies have examined the PKs of long-acting insulin in diabetic patients with CKD. Insulin requirements show a biphasic course in patient with diabetes and CKD. In the beginning, more insulin is needed to achieve glycemic control because of insulin resistance, while insulin requirements become lower or even has to be stopped, if necessary, in advanced renal failure with creatinine clearance below 50 mL/min. The insulin requirements also change in CKD patients on hemodialysis, as it improves

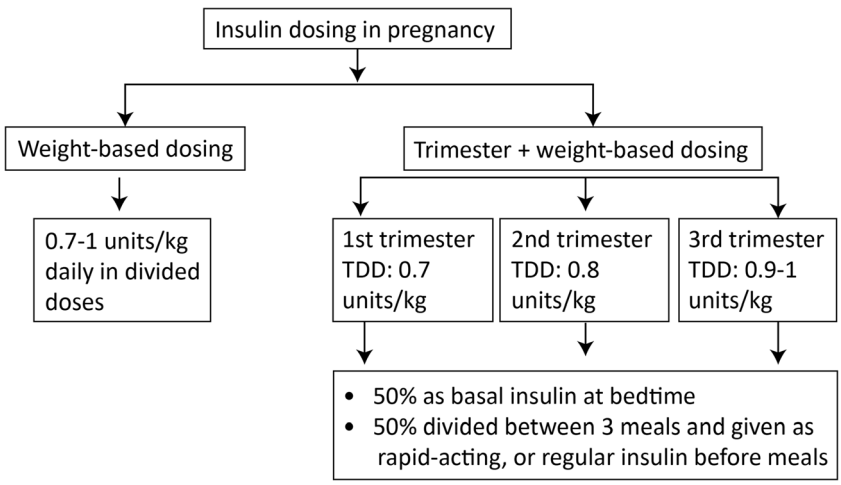

Fig. 12 Insulin regimens and dosing in pregnancy. TDD, total daily dose; NPH, neutral protamine Hagedorn; IAsp, *insulin* aspart; ILis, *insulin* lispro

Table 8 Glycemic targets for renal patients

	HbA1c (%)	FPG (mg/dL)	2-h PPBG (mg/dL)
Normal GFR, microalbuminuria +	6.5–7	80–120	< 180
Pre-dialysis (CrCl < 10)	< 7.5	100–120	< 180
Dialysis	7.5–8	100–140	< 180
Post renal transplant	6.5–7	80–120	< 180

Adapted from RSSDI clinical practice recommendations for management of in-hospital hyperglycemia—2016 [145]

insulin sensitivity and liver metabolism [145]. Consensus statement on insulin therapy in CKD (published in 2017) also recommends no dose adjustment in patients with GFR > 60 mL/min. However, it recommends a reduction to 75% and 50% in insulin TDD for patients with GFR between 15 and 60 mL/min and < 15 mL/min, respectively [146]. Moreover, renal-compromised patients have less stringent glycemic targets as shown in Table 8 [145].

In non-critical care situation, the preferred insulin is short-acting insulin analog over regular insulin. Patients with normal eGFR and albuminuria or transplant recipients may need tighter control albeit without the risk of hypoglycemia [147]. MDI insulin therapy with rapid-acting insulin analogs is ideal for patients with advanced CKD (eGFR < 30 mL/min) to deal with poor and unpredictable food intake, nausea, and vomiting. For those with eGFR between 30 and 60 mL/min, MDI insulin therapy with one to two basal insulin injections and two to three rapid-acting insulins (preferably analogs) may be required [145].

Insulins lispro, aspart, and glulisine are short-acting insulin analogs with very similar PK profiles. In the diabetic population with ESRD undergoing hemodialysis, lispro insulin provided better glycemic control and improves quality of life [148, 149]. A study in patients with T2DM and severe renal insufficiency suggested that insulin glulisine can effectively suppress postprandial hyperglycemia without prolonged hypoglycemic action [150]. Further, the PK of short-acting insulin aspart was not affected in a clinically significant manner by renal impairment, hepatic impairment, or BMI [151].

In 2012, a study bt Niafer et al. reported safety and good tolerance of insulin glargine added to regular insulin in patients with T2DM and diabetic nephropathy [152]. Another study by Kulozik and Hasslacher reported low-dose requirements of insulin glargine and detemir in T1DM patients with renal dysfunction. The insulin dose requirements were 29.7% lower in glargine-treated patients and 27.3% lower in detemir-treated patients at a GFR of < 60 mL/min compared with the dose requirements at an eGFR of > 90 mL/min [153]. A subgroup analysis of the ORIGIN data has identified CKD (in both mild and moderate stages) as a significant risk factor for macrovascular complications in people with early dysglycemia. Moreover, these results were not impacted by the use of basal insulin glargine compared with standard treatment [154]. AWARD-7, a multicentre, open-label trial, compared dulaglutide in two different doses to insulin glargine in patients with T2DM and moderate-to-severe CKD (n = 577). The effect on glycemic control of once-weekly dulaglutide was noninferior to that achieved with insulin glargine. Lesser declines in eGFR were also noted with dulaglutide in this study [155, 156]. A study evaluating the PKs of insulin degludec in 30 patients (n = 6 per group) with normal renal function; mild, moderate, or severe renal impairment; or end-stage renal disease (ESRD) undergoing hemodialysis reported no need for dose adjustment in patients with impaired renal functions [157].

A meta-analysis of non-randomized clinical trials conducted in 2015 by Almalki and coworkers found adequate and superior glycemic control with the use of intraperitoneal (IP) insulin compared with treatment with conventional subcutaneous insulin. However, IP insulin adversely affected plasma lipid profile, possibly contributing to increased CV risk. The authors of this review suggested need for further studies to assess the long-term safety of this approach [158]. Analysis of the SAIL patient-linked dataset reported a linear association between CKD severity and insulin use; however, approximately 54% in the severe CKD group received insulin [159].

Although insulin remains the first choice of treatment for patients with uncontrolled diabetes and CKD, few OADs can be used safely after dose adjustment in these patients for milder hyperglycemia. The target as well as threshold to start antihyperglycemic agents in patients with diabetes and CKD is HbA1c > 7% [147, 160].

Recommendations from RSSDI for patients with CKD

- CKD risk and progression can be minimized by optimizing blood glucose and controlling blood pressure.
- All insulins are considered safe across the spectrum of CKD. However, insulin doses in CKD may need to be reduced with lower eGFR levels.
- Prompt adjustments with reduction to 75% and 50% are often necessary in insulin TDD depending on the GFR between 15 and 60 mL/min and < 15 mL/min, respectively. However, no dose modification is suggested in patients with GFR > 60 mL/min.
- Doses of oral agents may be modified based on eGFR calculation where necessary.
- Among basal insulins, insulins detemir and glargine appear to be safe and effective.
- Among prandial insulins, both regular insulin and rapid-acting insulin analogs appears to be safe and effective.
- Rapid-acting insulin analog/basal insulin analog may be preferred over conventional insulin.

Insulin therapy during religious fasts including Ramadan

The use of insulin during prolonged fasting carries an increased risk of severe hypoglycemia in patients with both T1DM and T2DM. IDF-DAR Practical Guidelines recommend using insulin analogs (basal, prandial, and premix) over regular human insulin due to their lower rates of hypoglycemia [161]. Current ISPAD Clinical Practice Consensus Guidelines recommend a reduction to 60–70% of the basal insulin or to 70–85% of the pre-fasting TDD in patients treated with MDI [162]. About 20–40% dose reduction is recommended in the last 3–4 h of fasting for those treated with insulin pumps. The South Asian Guidelines recommend a reduction in basal insulin dose by 10–20% during the fasting days of Ramadan [163]. However, these recommendations of South Asian Guidelines were not based on data from large study cohorts or randomized controlled studies. Steps for insulin adjustments and dose titrations during religious fasts are shown in Fig. 13. In 2009, a multinational study by Salti et al. reported a significant increase in mild hypoglycemic events from 156 pre-Ramadan to 346 during Ramadan ($p < 0.001$) in patients treated with a combination of insulin glargine and glimepiride [164]. Two studies by Bakiner et al. and Cesur et al. found insulin glargine to be safe to use during Ramadan, without significant increases in hypoglycemia when compared with those taking OADs or non-fasting individuals [165, 166]. A comparison of insulin lispro and soluble human insulin revealed that the postprandial rise in BG levels after iftar and the rate of hypoglycemia were both significantly lower in those who received insulin lispro before iftar ($p < 0.01$ and $p < 0.002$, respectively) [167]. A comparison of human insulin 30/70 (30% short-acting soluble human insulin/70% intermediate-acting neutral protamine Hagedorn [NPH]) with insulin lispro Mix25 (25% short-acting lispro/75% intermediate-acting lispro protamine) during Ramadan found that overall glycemic control was better among patients on insulin lispro Mix25 ($p = 0.004$) [168]. Similarly, in another study, regular human insulin with NPH (30:70) in the morning and insulin lispro Mix50 (50% lispro/50% lispro protamine) in the evening improved glycemic control without increase in hypoglycemic events compared with regular human insulin with NPH (30:70) given twice daily [169].

Recommendations from RSSDI for Insulin therapy during religious fasts including Ramadan

- T2DM patients on intensive insulin therapy should abstain from fasting.
- Physician suggestions should be taken into consideration regarding the change in dose and timing of insulin injections during fasting period.
- Use of rapid-acting insulin analogs may be preferred in patients with T2DM who fast during Ramadan over regular human insulin due to lower risk of hypoglycemia and postprandial glucose excursions.

Insulin therapy in CVD patients

Guidelines are inconclusive regarding the use of insulin in patients with cardiovascular disease (CVD). The relationship between insulin and CVD is complex. Patients with diabetes are at increased risk for CVD and associated clinical complications. Large clinical studies, such as the Veterans Affairs Diabetes Trial (VADT), Action in Diabetes and Vascular Disease-PreterAx and DiamicroN Controlled Evaluation (ADVANCE), and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials, have shown mixed results for CV outcomes [170–172]. The VADT found no difference between the intensive group and the standard therapy group for a time to the first major CV event, though more frequent hypoglycemic events were noted in the intensive group (17.6 vs. 24.1%) [170]. The ACCORD trial also found no significant reduction in major CV events with intensive therapy [171]. In the ADVANCE trial, intensive glucose control significantly reduced both major macrovascular and microvascular events in patients with T2DM [172].

The ORIGIN trial has reported a neutral effect of insulin glargine on CV outcomes; though, it increased hypoglycemia and weight gain [173]. In 2018, the DEVOTE trial demonstrated that ultra-long-acting insulin analogs like insulin degludec were comparable with that of insulin glargine U100 concerning CV outcomes in patients with T2DM; though, the risk for severe hypoglycemia was less with insulin degludec. Thus, insulin degludec might be preferred in those with CVD, those at risk for severe hypoglycemia, and/or those with CKD [174].

Outcomes of the randomized pragmatic real-life clinical trial achieve control consistently favored Gla-300 in pts without CVD. In CVD pts, Gla-300 was similar to standard of care

Switch to insulin analogue

Basal insulin	▪OD - Reduce dose by 15-30% at iftar. ▪BID - Usual morning dose at iftar. Reduce evening dose by 50% at suhoor
Bolus insulin	▪Normal dose at iftar. Omit lunch-time dose. Reduce suhoor dose by 25-50%
Premixed insulin	▪OD - Normal dose at iftar ▪BID - Usual morning dose at iftar. Reduce suhoor dose by 25-50% ▪TID - Omit afternoon dose. Adjust iftar and suhoor doses as described above

Every three days, dose adjustment should be made according to BG levels

Fasting/ Pre-iftar/ Pre-suhoor BG	Pre-iftar**	Pre-iftar**/ Post-suhoor***	
	Basal insulin	Short-acting insulin	Premixed insulin
<70 mg/dl or symptoms	↓4 units	↓4 units	↓4 units
72-90 mg/dl	↓2 units	↓2 units	↓2 units
92-126 mg/dl	No change	No change	No change
128-200 mg/dl	↑2 units	↑2 units	↑2 units
>200 mg/dl	↑4 units	↑4 units	↑4 units

Insulin pump	▪Basal rate - Reduce dose by 20-40% in the last 3-4 h of fasting. Increase dose by 0-30% early after iftar ▪Bolus rate - Normal carbohydrate counting and insulin sensitivity principles apply

Fig. 13 Insulin adjustments and dose titrations during religious fasts including Ramadan. BG, blood glucose; OD, once daily; BID, twice daily; TID, three times a day

(SOC) BIs (glargine 100 U/mL and detemir) in composite endpoint and HbA1c target ($p = 0.34$) attainment at 12 months while avoidance of serious hypoglycemia (BG < 54 mg/dL) showed a trend favoring Gla-300 [175].

Recommendations from RSSDI for insulin therapy in CVD patients

- In case there is inadequate control with OADs, the addition of basal insulin shall be considered.
- If the glycemic goal is not achieved after the addition of basal insulin, then a basal plus/premix regimen may be considered before proceeding to a basal-bolus insulin regimen.

Insulin therapy in hepatic impairment

ADA 2007 guidelines have highlighted the importance of insulin and suggested frequent dose titrations and glucose monitoring in patients with T2DM and chronic liver disease (CLD) [176]. Indian consensus 2017 recommends newer insulin analogs as their PK remains unaltered in CLD patients and also has a low risk of hypoglycemia. It also suggested that the dose should be titrated frequently in CLD patients [177]. Expert opinion by Scheen et al. mentions that insulin does not exert hepatotoxic effects and can be used in all stages of CLD [178]. However, in cirrhotic patients, the dose should be carefully adjusted with frequent blood glucose monitoring for optimal glycemic control without hypoglycemia. Insulin may be the safest agent and dose adjustment should be individualized. Insulin therapy can be used in all stages of CLD although clinical studies are scarce. No single study reports extensive experience with insulin analogs in CLD patients [179]. In one study examining the effect of hepatic impairment on the PKs of insulin degludec, a single subcutaneous dose of 0.4 U/kg insulin degludec was administered to 24 individuals (allocated to four groups based on their hepatic impairment level). The results showed no difference in maximum insulin degludec concentration (C max), area under the 120-h serum insulin degludec concentration-time curve ($AUC_{0–120}$), and apparent clearance (CL/F) for individuals with impaired versus normal hepatic function [180]. Another study by Holmes et al. examining the effect of hepatic impairment on the PKs of insulin aspart reported no correlation between the degree of hepatic impairment and any PK variable [151]. Insulin detemir was found less efficacious in two patients with significant NAFLD and hypertriglyceridemia. In such patients, very high dose is required to achieve glycemic control [181].

The rapid-acting insulin analogs can be given just after meals. This is of benefit to CLD patients as they may have nausea and reduced appetite. Thus, depending on the intake, such patients with CLD have the option of using rapid-acting insulin analogs just after their meals [177].

Recommendations from RSSDI for insulin therapy in hepatic impairment

- Use of insulin analogs should be considered in T2DM patients with hepatic impairment for improved glycemic control with low risk of hypoglycemia.

Insulin therapy in hospitalized patients

Guidelines from the ADA 2019 and RSSDI 2016 recommend basal insulin or a basal plus bolus correction insulin regimen for noncritically ill hospitalized patients with poor oral intake and an insulin regimen with basal, prandial, and correction components for noncritically ill hospitalized patients with good nutritional intake [145, 182]. ADA guidelines also suggest avoiding sliding scale insulin in the inpatient hospital setting [182]. Initial and maintenance insulin dosing protocol for hospitalized patients with diabetes should be adjusted based on RSSDI clinical practice recommendations for management of in-hospital hyperglycemia—2016 as shown in Table 9 [145]. The benefits of intensive insulin therapy in surgical patients as compared with medical patients have been elucidated in a meta-analysis [183, 184]. However, the Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study found an increase in 90-day all-cause mortality (HR 1.14; 95% confidence interval [CI] 1.02–1.28; p = 0.02) among critically ill medical and surgical patients randomized to the intensive glycemic control arm [183]. Furthermore, an increased risk of hypoglycemia was found with intensive insulin therapy in the ICU setting. Therefore, maintaining a BG level < 180 mg/dL is a safe target in critically ill hospitalized people with diabetes [185].

Recently, a study comparing basal plus correction with basal-bolus (plus correction) insulin regimen reported no difference in FBG or rates of hypoglycemia [186]. Another study also found no difference in BG levels or rates of hypoglycemia when comparing insulin glargine with detemir, when used as the basal insulin in a basal-bolus program [185, 187].

Recommendations from RSSDI for insulin therapy in hospitalized patients

- For majority of critically ill patients in ICU, insulin infusion should be used to control hyperglycemia.
- BG > 180 mg/dL should trigger insulin initiation.
- Once IV insulin started, glucose level should be maintained between 140 and 180 mg/dL.
- The exact protocol is probably less important; what is important is its presence in an institution and adaptation to the individual hospital needs.
- The protocol in Table 7 above may be adapted as recommended by RSSDI inpatient hyperglycemia guidelines 2016.
- Discontinuation of IV insulin often leads to rebound hyperglycemia. Hence, intravenous to subcutaneous insulin transition should be made carefully and only after it is evident that the patient exhibits stable glycemic control.
- Transition is more likely to be successful if blood sugar levels are between 140 and 180 mg/dL with constant insulin drip rate.
- It should be ensured that there is continuity between IV insulin infusion and the first dose of SC insulin.
- The total daily insulin requirement calculation can be best ascertained during a time interval of 4–6 h during which the blood glucose values are at goal and IV insulin rates are not particularly elevated or variable.
- Regular insulin or rapid-acting analogs should be used for the bolus/prandial insulin and the supplemental insulin. The basal insulin requirement should be met using NPH or insulin detemir, glargine, or degludec.

Driving and insulin-treated diabetes

ADA guidelines recommend assessing people with diabetes individually, taking into account their medical history as well as the

Table 9 Initial and maintenance insulin dosing protocol

Initial infusion dosing		Maintenance infusion dosing			
Priming bolus	0.1 U/kg body wt	BG (mg/dL)	↑BG from prior BG	BG ↓ < 30 mg/dL from prior BG	BG ↓> 30 mg/dL from prior BG
Infusion initiation (U/h)	BG divided by 100	≥ 241	↑rate 3 U/h	↑rate 3 U/h	No change
		211–240	↑rate 2 U/h	↑rate 2 U/h	No change
Rate adjustment (monitor BG hourly)		181–210	↑rate 1 U/h	↑rate 1 U/h	No change
BG ↓> 30 mg/dL	Same infusion dose	141–180	No change	No change	No change
BG ↓< 30 mg/dL	Increase infusion dose	110–140	No change	↓rate by 50%	↓rate by 50%
BG ↑above baseline BG	Increase infusion dose	91–109	No change	Hold insulin*	Hold insulin*
		71–90	Hold insulin**		
		≤ 70	Hold insulin, give 25% dextrose (100 − BG) × 0.8**		

Adapted from RSSDI clinical practice recommendations for management of in-hospital hyperglycaemia—2016

*Check BG level at 1 h. Restart infusion at 50% of the previous rate when BG increases > 140 mg/dL

**Check BG level at 30 min until BG > mg/dL and then check BG level at 1 h. Restart infusion at 50% of the previous rate when BG increases > 140 mg/dL

Example: BG = 40 mg/dL, give (100 − 40) × 0.8 = 60 × 0.8 = 48 mL of 25% dextrose IV and check BG after 15 min

potential related risks associated with driving. Although the Third European Commission Driving Licence Directive has led to the introduction of stricter rules for group 1 licence holders, this has removed the blanket ban on those with insulin-treated diabetes driving lorries and passenger-carrying vehicles (a group 2 license holders) [188]. A global survey of licensing restrictions for drivers with diabetes reported absolute no restrictions (100%) in South East Asia [189]. Drivers with T1DM are at an increased risk for driving mishaps compared with drivers with T2DM [190]. In one of the questionnaire-based studies, 40% of participants with insulin-treated T2DM reported at least one episode of disrupted driving associated with hyperglycemia over 1 year compared with 8% of participants with T1DM [191]. In 2018, a cross-sectional study reported that majority of people with insulin-treated diabetes mellitus (ITDM; 76.5%) never discussed topics regarding diabetes and driving with their healthcare professionals (HCPs). Three factors were associated with a higher risk of motor-vehicle collisions among participants with ITDM: (a) being on a basal/bolus regimen, (b) never having a discussion regarding diabetes and driving with their HCPs, and (c) having experienced hypoglycemia during driving [192]. A cross-sectional study was conducted among healthcare providers working at 4 tertiary hospitals in Riyadh, Saudi Arabia, between April 2016 and December 2016 using a self-administered questionnaire to assess their knowledge and awareness of the recommendations for drivers with insulin-treated diabetes. 70.2% were aware of recommendations for drivers with insulin-treated diabetes. However, the need to check blood glucose levels before driving was underestimated by 30.2%. [193].

Recommendations from RSSDI for driving and insulin-treated diabetes

- Healthcare professionals should educate the insulin-treated drivers about the risk of severe hypoglycemia.
- Blood glucose level should be monitored no more than 30 min before each drive and at least as often as once every 2 h of a journey.
- Blood glucose level ≥ 90 mg/dL could be considered as a safe level for driving.

Post-transplantation diabetes mellitus (PTDM or NODAT)

For the management of late-PTDM, lifestyle modification > oral antidiabetic therapy > insulin is an appropriate stepwise approach. However, the *reverse* of this sequence is the most appropriate management for patients with immediate post-transplant hyperglycemia. In the early post-transplant period, insulin is the only safe and effective agent in the context of high glucocorticoid doses and acute illness. In a small randomized controlled trial of 50 renal transplant recipients, Hecking et al. reported that early basal insulin used to treat post-transplant hyperglycemia (< 3 weeks) significantly decreased the odds of developing post-transplant diabetes mellitus (PTDM) within the first year by 73% [194]. Hermayer et al. comparing intensive glycemic control with intravenous (IV) insulin and standard of care with sc insulin reported no difference for delayed graft function (p = 0.46) in the 72 h after transplant among kidney transplant recipients. However, greater risk of a rejection episode (p = 0.012) and hypoglycemic events (p = 0.08) was found in those treated with intensive glycemic control. It is important to note this study only involved patients with established pretransplant diabetes [195]. In the setting of heart transplantation, one retrospective study demonstrated that IV and subcutaneous (SQ) insulin protocols with a glucose target of 80–110 mg/dL [4.5–6.1 mM] could safely be implemented in both patients with and without pretransplant diabetes [196].

Table 10 Compatibility of insulin with various IV fluids

	Normal saline	Ringer solution	5% dextrose
Regular	✓	✓	✓
Basal	×	×	×
Premix	×	×	×
Aspart	✓	✓	✓
Lispro	✓	✓	✓
Glulisine	×	×	✓

Recommendations from RSSDI for PTDM or NODAT

- Insulin therapy should be preferred during the first 1–2 months of time period after transplantation.
- Management of late-PTDM should be done in an appropriate way such as lifestyle modification > oral antidiabetic therapy > insulin.

Post-immunotherapy new-onset diabetes

New-onset diabetes mellitus associated with immunotherapy generally occurs in less than 1% of patients. This condition often presents as DKA, a medical emergency requiring immediate treatment. In 2018, an article by Sanjay Kalra on post-immunotherapy new-onset diabetes (PINOD) suggests insulin as the treatment of choice in these patients [197]. This article also suggests the use of metformin, if it is well-tolerated and is not contraindicated [197].

Recommendations from RSSDI for PINOD

- Insulin be the drug of choice in this form of insulinopenic diabetes
- Metformin should be used, provided it is not contraindicated and is well-tolerated

General considerations for insulin therapy

Insulin compatibility

Knowledge regarding compatibility of insulin with various IV fluids is mandatory for today's physician to achieve the desired therapeutic effect in all diabetic patients without producing toxic effects in any patients (Table 10) [198].

Insulin concentrations and strengths

With the commonly available U-40 and U-100 insulins, it is not always possible to satisfy the needs of insulin-resistant patients requiring a large volume of insulin. Also, large volumes of low-strength insulins can lead to erratic absorption and unpredictable effect. For these reasons, several concentrated insulins were developed to overcome severe insulin resistance and address the needs of individuals requiring a large volume of insulin and include agents like degludec U200, glargine U300, lispro U200, regular insulin U200, and regular insulin U500. U200 formulations of glargine, NPH insulin, and 30:70 insulin are also manufactured by Wockhardt [199].

Recommendations from RSSDI for insulin concentrations and strength

- Concentrated basal insulin offers the advantages of low injection volume leading to less pain, low variability, and lesser risk of hypoglycemia and can be prescribed as an alternative to U100 basal insulin.
- In those patients requiring very high units of insulin, pump therapy should be considered as one of the best options if eligible and affordable.
- 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.

Insulin delivery devices

Insulin syringes remain the most common way to deliver insulin subcutaneously; though, their capacity should be chosen based on the dose of insulin. Other factors that need to be taken into consideration while selecting insulin syringe include needle gauge and needle length as longer needles increase risks for intramuscular injections [200]. A 6-mm needle, the shortest needle available on an insulin syringe, not only minimizes the risk for intramuscular injections but also helps to reduce pain and even simplify the injection technique. In adolescents or adults, needles longer than 6 mm are not recommended [201, 202].

Recommendations from RSSDI for insulin delivery devices

- Insulin syringes or pens may be used for delivery with consideration of patient's preference, type of insulin, dosing regimen, cost, and self-management capabilities.
- Insulin pens may be preferred due to accuracy of dosing and convenience of injection.
- Delivery of insulin via insulin pens or injections may be considered for people with vision impairment or dexterity issues to facilitate the administration of accurate insulin dose.

Insulin transport and storage

Forum for Injection Technique and Therapy Expert Recommendations (FITTER) India 2017 recommends following specific storage conditions provided by the manufacturer for insulin, though ideally should be stored in a cool (below 30 °C) and dark place [7]. East Africa Diabetes Study Group (EADSG) guidelines recommend a temperature range of 2–8 °C for the suitable container used for transport of insulin. Exposure of insulins to temperatures outside the recommended ranges can reduce their potency and effectiveness. Therefore, maintaining the cold chain is very important while transporting insulin from the production facility to the distributor's storage facility [44]. If refrigeration is not available, unopened insulin vials may be stored in a pot with sand or may be submerged in water [203]. Contamination of insulin and resultant abscesses at the injection site is a known complication if the cold chain is not properly maintained.

Suitable cool boxes and gel packs should be used to maintain the temperature of the insulin-transporting container between 2 and 8 °C. It should not be transported in containers having temperatures below 2 °C, or above 32 °C [204].

Recommendations from RSSDI for insulin transport and storage

- Specific storage conditions provided by the manufacturer in the package inserts should be followed.
- If no extremes of temperatures are envisaged, transporting insulin from a health facility to home transportation can be done without an icepack. If uncertainty exists about an exposure to high temperatures (> 30 °C), it is advised to transport insulin on an ice pack.
- Insulin vials can be transported by submerging in water or keeping insulin in a pot with sand, if refrigerator is unavailable.

Injection sites

FITTER India guidelines recommended the abdomen, thigh, buttock, and upper arm as injection and infusion sites (Fig. 14). Insulin was injected in the upper arm, abdomen, and thigh

by 71.43%, 28.57%, and 5.36% of Indian patients, respectively. All the patients rotated injection sites [7].

Recommendations from RSSDI for injection sites

- Abdomen, thigh, buttock, and upper arm are the recommended infusion and injection sites.

Injection site rotation

According to FITTER India, the systematic rotation of insulin injection sites should be done to optimize insulin absorption, maintain healthy injection sites, and reduce the risk of lipohypertrophy (LH) [7]. To avoid glucose variability, the same site at the same time each day and injection site rotation should be practiced to avoid glucose variability and LH (same time same site rule) [7].

For each injection, a new site should be chosen. This ensures stable insulin absorption. This can be done by dividing the injection site into quadrants (abdomen) or halves (thighs, buttocks, and arms). One quadrant or half should be used for 1 week and then move either in a clockwise or in an anticlockwise fashion to another quadrant or half, next week. A distance of at least 1–2 cm should be kept from the previous injection site while selecting a new injection site. Do not inject in the area of LH, inflammation, edema, or infections. Annually, the HCPs should review the site rotation scheme with the patient [7].

Recommendations from RSSDI for injection site rotation

- Systematic switching of the injections from one site to another site and within the injection site helps in maintaining healthy injection sites, optimize insulin absorption, and reduce the risk of LH.
- The difference between new injection site and previous injection site should be at least 1–2 cm.
- Site rotation scheme should be reviewed by the healthcare professionals with the patient at least once a year.

Needle length

FITTER India recommends the use of a 4-mm needle with pens and a 6-mm needle with syringes. Injections with syringe needle should always be given into a lifted skinfold at 90 in children ≥ 6 years old, adolescents, or slim to normal-weight adults [7].

A 4-mm needle is considered the safest needle for all diabetic people regardless of age, sex, ethnicity, or BMI, with little risk of IM or intradermal injection [7].

In 2015, a randomized controlled study by Bergenstal et al. reported equivalent glycemic control with the 4-mm pen needle compared with 8.0- and 12.7-mm pen needles, respectively, in 274 obese (BMI ≥ 30) patients with diabetes with less pain ($p < 0.05$) and no increase in leakage [205]. A 5-mm needle may also be used in obese individuals [7]. Only a 4-mm needle should be inserted in children aged ≤ 6 years and very thin adults by lifting a skinfold at 90°. Others may inject using the 4-mm needle without lifting a skinfold [7].

Recommendations from RSSDI for needle length

- 4-mm needle with pens and 6-mm needle with syringes should be used in children, adolescents, and adults.
- In children, extremely lean and elder patient's skinfold is required when using 5- and 6-mm needle, but in children, adolescent, and adults, an injection angled at 45° is required while using 6-mm needle.
- In adults, injection into limbs and slim abdomen warrants the need for a skinfold with needles longer than the 5 mm.
- Shorter needle should be inserted perpendicularly to the skin surface.

Injection site complications

Common complications of subcutaneous insulin injection include LH. Other frequently encountered local allergic reactions to insulin are usually erythema, pruritus, and induration [206].

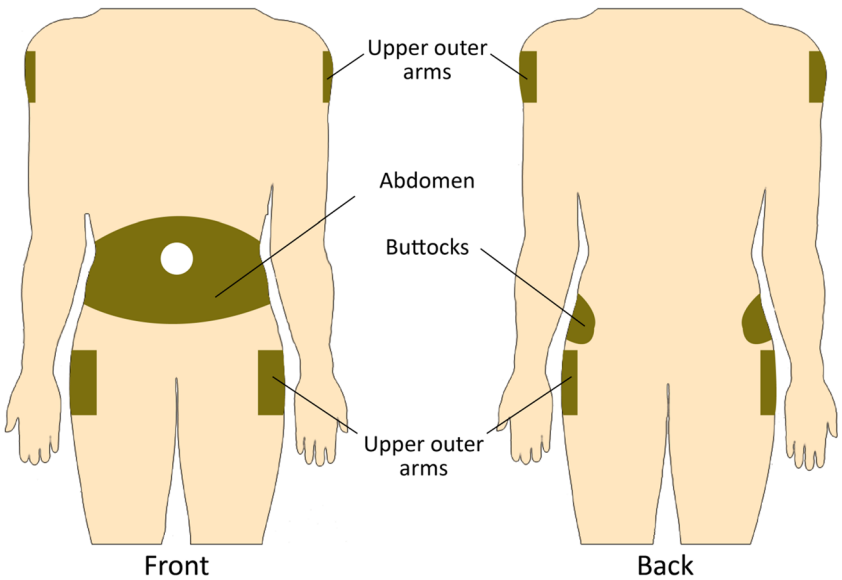

Fig. 14 Insulin injection sites.

Lipohypertrophy

Lipoheypertrophy, a rubbery swelling in the subcutaneous (SC) tissue, is a common complication of insulin therapy. In 2018, a systematic review and meta-analysis involving 26 studies and 12,493 participants found 38% pooled prevalence levels of lipoheypertrophy (LH) among insulin-injecting diabetes patients. Higher prevalence was found among patients with T2DM as compared with patients with T1DM (49%, 95% CI 23–74% vs. 34%, 95% CI 19–49%) [207]. In 2018, two Indian studies reported more than 60% of their prevalence among insulin users [208, 209]. FITTER India recommends regular inspection of injection site, single use of needle, proper injection site rotation, use of larger injection zones, and avoiding repeated use of the same site to prevent the development of LH. For management, it recommends a decrease in insulin dose when shifting to normal SC tissue and regular inspection by both HCPs and patients with diabetes [7].

Pahuja et al. found that out of 68% of patients who had LH, only 26% always rotated injection sites and 16% changed needles more than half of the time in the week. Further, 77% of patients with LH were unaware of the condition. Furthermore, it was associated with an increased duration of diabetes and insulin injection therapy and a higher insulin dose per day (each $p < 0.05$) [210].

Proper injection site rotation, use of larger injection zones, and avoiding needle reuse can lessen the development of LH [211]. In 2017, an ITQ survey throughout India involving 1011 patients reported that 90% of LH lesions had resolved and glycemic control had significantly improved after 3 months of receiving specific instructions from diabetic nurses to rotate injection sites and not to reuse needles [212]. However, other workers reported no effect of avoiding reuse of needles [208]. Injection technique (IT) education, particularly concerning the use of shorter needles, has been shown to effectively prevent LH in prospective randomized controlled trials [213].

Recommendations from RSSDI for LH

- Regular inspection and palpation of insulin sites should be performed.
- Reuse of needles and injection site should be avoided.
- Follow correct site rotation policy.
- Decrease in the insulin dose is required before switching site of injections from LH to normal tissue, but it varies from one individual to another and should be monitored by frequent blood glucose measurements.

Bleeding and bruising

Insulin needles can occasionally produce bruising or bleeding after hitting a blood vessel or a capillary bed. FITTER India recommends only regular assessment of site as it appears to have no adverse clinical consequences [7]. As shown by numerous studies, bleeding and bruising incidents are greatly reduced with the use of shorter needles [214].

Recommendations from RSSDI for bleeding and bruising

- Local bruising and bleeding do not affect the clinical outcomes or the absorption of insulin.
- In case bleeding and bruising are frequent, the injection technique should be carefully assessed and presence of a coagulopathy, use of anticoagulant, or antiplatelet agents should be checked.

Needle stick injuries

Needle stick injuries (NSIs) are common among HCPs and warrant training on preventive methods. Zhao et al. conducted a large online survey among hospital nurses in China from October 2016 to February 2017 and found that prevalence of at least one episode of NSI was about 39.1%, of which 3.2% were having hepatitis B virus infection and 0.9% were having hepatitis C virus infection [215]. FITTER India recommends the use of shorter needles, education, and training of HCPs and avoiding reuse of needles [7].

Recommendations from RSSDI for NSIs

- Healthcare professionals should be trained and educated on how to minimize risk, by following optimal technique and using available safety devices.
- Short needles should be used to avoid local bruising and bleeding.
- Needles should not be reused.

Diet/exercise and alcohol

ADA guidelines 2019 recommend education for people with T1DM and T2DM on how to use carbohydrate, fat, and protein content of food to determine mealtime insulin dosing. Alcohol consumption may increase the risk for hypoglycemia in people with diabetes, especially if taking insulin or insulin secretagogues; hence, guidelines also recommend education and awareness about recognition and management of delayed hypoglycemia in people consuming alcohol [216].

Evening-time exercise is a frequent cause of severe hypoglycemia in T1DM, fear of which deters participation in regular exercise. In 2015, Campbell et al. have demonstrated that exercise-induced hypoglycemia can be avoided, without exposure to hyperglycemia, when people with T1DM employ a combined basal-bolus insulin reduction and low GI carbohydrate feeding strategy. This strategy does not significantly augment ketonemia or cause other metabolic disturbances [217]. Several other studies have also demonstrated that it is possible to achieve euglycemia early after exercise by making mealtime adjustments to both rapid-acting insulin

administration and postexercise carbohydrate composition. Postexercise hyperglycemia, following high-intensity interval training (HIIT) in patients with T1D, is also largely underrecognized by the clinical community and generally undertreated. Recently, the FIT study conducted by Aronson et al. comparing four multipliers (0, 50, 100, or 150%) of an individual's insulin correction factor (ICF) to treat post-HIIT hyperglycemia reported optimal plasma glucose (PG) reduction, with minimal hypoglycemia, in the 100 and 150% correction arms [218].

In patients with unstable T2DM on insulin, the use of low carbohydrate dietary approaches, including ketogenic diets, may cause hypoglycemia, complicating the matching of glucose self-monitoring to medical supervision of insulin dose adjustment. If the blood glucose level is < 72 mg/dL (4.0 mmol/L) and the patient is symptomatic and awake and can swallow, manage according to the rule of 15 (provide 15 g of quick-acting carbohydrate; wait 15 min and repeat blood glucose check; if the patient's next meal is more than 15 min away, provide some longer-acting carbohydrate) [219].

Moderate alcohol intake does not have major detrimental effects on long-term blood glucose control in people with diabetes [220]. Moderate alcohol consumption has been reported to decrease the risk of diabetes by approximately 30% [221]. It was only in the instances of prolonged heavy alcohol intake (e.g., ~ 60 g/day for men; 50 g/day for women) where alcohol had a deleterious effect [222, 223]. Another study by Turner et al. followed 6 men with T1DM from 5 PM to 12 PM the following day. The men received regular insulin injections before meals consumed at 6 PM and 8 AM as well as a basal insulin infusion overnight. At 9 PM, 3 h after the evening meal, 0.75 g/kg of wine was administered for 90 min. Blood glucose, alcohol, and insulin were measured throughout the evaluation. There were no significant differences in blood glucose in the evening or overnight observation periods. However, in the morning, fasting and postprandial blood glucose levels were significantly lower following consumption of alcohol and 5 individuals required treatment for hypoglycemia [224].

Recommendations from RSSDI for diet/exercise and alcohol

- Individuals diagnosed with T1DM and T2DM should be taught on how to use carbohydrate, fat, and protein counting to determine mealtime insulin dosing to improve glycemic control.
- Carbohydrate sources high in protein should be avoided in individuals with T2DM to treat or prevent hypoglycemia as ingested protein increases insulin response without increasing plasma glucose concentrations.
- Adults with diabetes are advised moderate alcohol intake (no more than one drink per day for adult women and no more than two drinks per day for adult men).
- Diabetic patient taking insulin or insulin secretagogues may be put to increased risk of hypoglycemia due to consumption of alcohol. Therefore, education and awareness regarding the recognition and management of delayed hypoglycemia are important.

Managing insulin resistance

ADA 2019 guidelines recommend aerobic and resistance exercises regularly regardless of diabetes type to decrease insulin resistance. Aerobic activity bouts should ideally last at least 10 min, with the goal of 30 min/day or more, most days of the week for adults with T2DM.

Insulin therapy is usually preferred in pregnant women with preexisting diabetes (both T1DM and T2DM) because OADs are generally insufficient to overcome the insulin resistance in pregnant women with T2DM and is ineffective in T1DM [216].

Hypoglycemia, weight gain, and other safety and psychosocial aspects

Hypoglycemia with insulin therapy

WHO guidelines recommend considering long-acting insulin analogs to manage blood glucose in adults with T1DM or T2DM who have frequent severe hypoglycemia with human insulin [225]. Clinically, hypoglycemia is characterized by low plasma glucose, physical symptoms like shaking and palpitations, and resolution of symptoms with treatment. Recommendations from the International Hypoglycemia Study Group regarding the classification of hypoglycemia in clinical trials are outlined in Table 11.

Hypoglycemia was found to be less frequent and less severe in patients with T2DM compared with patients with T1DM. The DCCT-like Kumamoto study reported only slight increase in mild hypoglycemia after intensive insulin therapy in T2DM patients [226]. However, the UKPDS study reported symptomatic hypoglycemia in about 30%, but severe hypoglycemia in only about 2% of diabetic patients [227]. Three studies in T2DM, The VADT, the ACCORD, and the ADVANCE trials, have greatly improved understanding between T2DM and cardiac risk [170–172]. The ACCORD and the ADVANCE trials have proved what seems to be a favorable adaptation to tighter glycemic control, likely due to episodic moderate hypoglycemia.[171, 172]

Potentiating factors include strenuous or unplanned exercise, excess alcohol without adequate carbohydrate consumption, an abrupt switch to low-starch foods, errors in dose of insulin, timing, or delivery of insulin, injection into LH sites; concomitant administration of OADs in patients with T2DM; and comorbidities such as liver and kidney disease. Individuals with longer duration of diabetes, poor appetite or erratic lifestyles and eating patterns, neurocognitive decline, and significant weight loss and older patients are at a higher risk of hypoglycemia.

Table 11 Classification of hypoglycemia

Level	Glycemic criteria	Description
Hypoglycemia alert value (level 1)	≤ 70 mg/dL (3.9 mmol/L)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycemia (level 2)	< 54 mg/dL (3.0 mmol/L)	Sufficiently low to indicate serious, clinically important hypoglycemia
Severe hypoglycemia (level 3)	No specific glucose threshold	Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery

Recommendations from RSSDI for hypoglycemia with insulin therapy

- Consider insulin analogs to manage blood glucose in adults with T1DM or T2DM who have frequent severe hypoglycemia with human insulin.
- Periodic SMBG (≥ 3 times a day, preferably after meals) is necessary in patients who have frequent episodes of hypoglycemia.
- Other recommendations: regular checkup of injection site (erratic absorption can induce hypoglycemia), taking recommended doses at mealtimes, appropriate insulin dose adjustments before and after exercise, and ensuring easy accessibility of carbohydrate supplement and glucometer.
- Degludec and glargine U300 are newer long-acting basal analogs compared with existing basal analogs, detemir, and glargine U100, respectively, with more physiological basal profiles and provide a lower risk of nocturnal hypoglycemia.
- Insulin infusion pump therapy and CGM are useful adjuncts to the management of T1DM.

Impaired hypoglycemic awareness

Impaired awareness of hypoglycemia (IAH) is a frequent complication of insulin therapy. Approximately 50% insulin-treated patients with T1DM and T2DM report hypoglycemia awareness, and 15–25% of patients have a permanent IAH [228]. In patients with T1DM, degludec significantly lowered rates of confirmed nocturnal hypoglycemia when compared with glargine U100 (estimated rate ratio [degludec/glargine] = 0.75, 95% CI, 0.60–0.94). As compared with detemir, a 33% lower rate of nocturnal hypoglycemia was observed (estimated rate ratio [degludec/detemir] = 0.67, 95% CI, 0.51–0.88) [229, 230]. Pooled patient-level data for self-reported hypoglycemia from randomized controlled phase III trials in individuals with T2DM and T1DM further confirm a lowering of nocturnal hypoglycemia risk with insulin degludec compared with glargine [229]. However, the randomized head-to-head BRIGHT trial reported comparable rates of hypoglycemia with both Gla-300 and IDeg-100 insulin during the full study period but lower in favor of Gla-300 during the titration period [231]. A single study showed a clinical benefit at less than or equal to 6 months of education and relaxation of BG targets compared with insulin lispro/glargine in people with T1DM and IAH for QoL (DQOL). However, the evidence showed clinical harm of education and relaxation of BG targets for HbA1c, and the number of patients with altered hypoglycemia awareness.

The diabetes management in patients with IAH is time-consuming and expensive. Therefore, a step-by-step approach, from insulin personalization and therapeutic training to advanced medical technologies, should be recommended for these patients. Evidence from these is summarized in Table 12 [232–234].

Recommendations from RSSDI for IAH

- The following strategies may be considered to eliminate the risk of severe hypoglycemia and to attempt to regain hypoglycemia awareness:
  - Less stringent blood glucose targets with avoidance of hypoglycemia for up to 3 months
  - Education regarding CSII or sensor-augmented pump or CGM and follow-up for T1DM

Weight gain with insulin therapy

ADA guidelines recommend considering the effect of glucose-lowering medications on the weight of overweight or obese patients with T2DM before choosing the medicines. It has been suggested to minimize the use of medications whenever possible for comorbid conditions that are associated with weight gain. Weight gain with insulin therapy can be limited. Using the insulin formulations judiciously and using "insulin-sparing" agents such as metformin, GLP-1RAs, and SGLT-2i in T2DM will be a suitable approach.

A fixed insulin regimen can also lead to weight gain; e.g., a basal-only insulin regimen in individuals with T2DM is associated with less weight gain compared with complex insulin regimens (e.g., premixed or basal-bolus). "Weight-sparing" effect is shown by insulin detemir due to its unique hepatoselective action and influence on satiety centers in the central nervous system. In individuals with T2DM, clinical trials have shown a lower mean weight difference of 0.91 kg (95% CI, − 1.21 to − 0.61 kg) with insulin detemir compared with insulin glargine, despite similar HbA1c levels and similar rates of hypoglycemia [235]. Similarly, in children and adolescents with T1DM, no significant weight gain have been

Table 12 Impaired awareness of hypoglycemia: clinical evidences

Study	Intervention/comparison	Population	Score system used for IAH	Outcomes
Choudhary 2010[a]	Prospective case series (9–12-month follow-up)	n = 95 T1DM n = 74 normal awareness, n = 21 IAH	Gold score ratings used to define IAH (≥ 4)	3 times higher incidence of severe hypoglycemia was found in patients with IAH
Hendrieckx 2014	Retrospective case series	n = 422 completers T1DM adults IAH (gold): 20.5%	Gold	Severe hypoglycemia: 18.5% at least one event in past 6 months 46% who reported SH episode in past 6 months also reported IAH; only 7% had intact awareness
Schopman 2011	Prospective case control study (4-week follow-up)	n = 38 T1DM normal awareness (n = 19) patients and IAH (n = 19) patients	Gold score	IAH patients vs. normal awareness: NS difference in total no. of symptomatic hypoglycemic episodes Higher annual prevalence of SH: 53% vs. 5% SS higher incidence of severe events (p = 0.001).

HUN, hypoglycemia unawareness; *IAH*, impaired hypoglycemia unawareness; *SH*, severe hypoglycemia

[a] Kappa index of 1.0 = complete agreement

observed with the use of insulin detemir in comparison with NPH insulin [236].

Recommendations from RSSDI for weight gain with insulin therapy

- In obese patients with T2DM, selection of antihyperglycemic agents should be based on their effect on weight.
- Whenever possible, minimize the use of medications associated with weight gain.

Hypersensitivity reactions/allergy to insulin

Insulin allergy is a rare complication with a prevalence rate of around 2.4% in patients suffering from T1DM and T2DM [237]. Out of the 17 cases reported previously, six cases reported initial reaction to lispro, five to detemir, five to aspart, and one to glulisine. According to the literature published earlier, around 88.2% of the cases reported insulin allergy in patients with T2DM and only two of the cases occurred in patients with T1DM (11.8%). There was variability in the reactions presented by the patients ranging from a few days in one case to a few years in others [238].

Variations in the clinical presentation were also seen from local cutaneous lesions to anaphylactic shocks which were either IgE- or IgG-mediated. Type I allergy reactions are IgE-dependent which are induced by insulin molecule or other components and activate the allergy-related pathway. However, insulin allergy mediated by IgG has also been reported. Various confirmatory tests were performed in 14 of the 17 cases which included skin prick testing (29%), intradermal testing (53%), antibody testing (65%), skin biopsy (12%), and patch testing (12%). There were some cases where multiple testing methods were used, and in several cases (23.5%), the details of the management were not discussed (Table 13) [239–246].

Various management techniques used for the human insulin analogs hypersensitivity reactions included:

- Use of a desensitization strategy (35%)
- Conversion to other non-insulin therapeutic options (23.5%)
- Conversion to an alternative insulin (12%)
- Use of immunotherapy (6%)

Recommendations from RSSDI for hypersensitivity reactions/allergy to insulin

- Intradermal testing (IDT) has been suggested as a more accurate assessment for identifying an insulin hypersensitivity reaction.
- When performing confirmatory testing, reactions to common human insulin analog (HIA) excipients should also be assessed in order to rule out hypersensitivity to individual excipients.
- Management of HIA hypersensitivity reactions can be done with the help of insulin desensitization protocols.
- Patient's scenario should be taken into account before switching to other management strategies.
- A discussion with patient regarding treatment plan, including reassurances about the trial and error process and emphasizing the importance of conducting a rechallenge with the offending agent to assist in identifying the cause.

Diabetic ketoacidosis and hyperosmolar hyperglycemic state

Insulin administration by the intravenous, intramuscular, or subcutaneous routes is safe and effective for correcting DKA (Fig. 15). As per the guidelines for the management of DKA issued by the Joint British Diabetes Societies guidelines, IV insulin infusion should be done at a weight-based fixed rate until the ketosis has resolved. When the blood glucose falls below 250 mg/dL, 10% glucose should be added to allow the fixed-rate insulin to be continued. If already taking, long-acting insulin analogs such as insulin glargine or insulin

Table 13 Insulin hypersensitivity and management: clinical evidences

Author	Country	Age/gender/type of diabetes	Duration of therapy prior to reaction	Concurrent insulin	Reaction	Confirmatory tests perfomed	Management
Detemir							
Aujero et al. 2011	USA	39 years/F/T1DM	Not specified	Not specified	Systemic	-	Discontinue detemir; further management not discussed
Blumer	Canada	63 years/M/T2DM	15 months	Not specified	Localized	-	Switched to glargine
Sola-Gazagnes et al.	France	29 years/M/T2DM	12 days	Not specified	Localized	Intradermal testing	Discontinue detemir; further management not discussed
Aspart							
Xiong et al.	China	48 years/F/T2DM	4 days		Localized	Skin prick test	Discontinued novorapid; switched to novolin 30R
Oray et al.	Turkey	45 years/M/T2DM	-		Localized and systemic		Basal insulin glargine and nateglinide treatments
Lispro							
Andrade et al.	Portugal	69 years/M/T2DM	2 years	Protaminated lispro	Localized	Skin prick testing, antibody	Switched to oral therapy
Watanabe et al.	Japan	28 years/F/T1DM	1 month	Protaminated lispro	Localized	Intradermal testing, antibody	Switched to glulisine
Glulisine							
Heinzerling et al.	USA	60 years/M/T2DM	5 months	Not specified	Not specified	Intradermal testing, antibody	Immunotherapy with regular insulin and antihistamine

detemir should be continued in usual doses [247]. In 2018, Razavi et al. compared the safety/efficacy of intermittent subcutaneous rapid-acting insulin aspart with the standard low-dose intravenous infusion protocol of regular insulin in 50 children/adolescents with mild/moderate diabetic ketoacidosis. The mean total dose of insulin units needed for treatment of diabetic ketoacidosis in intervention was lower than controls ($p < 0.001$). Subcutaneous insulin treated moderate DKA with faster recovery/shorter hospital stay [248]. In critically ill patients and those with a reduced level of consciousness (mentally obtunded), continuous intravenous infusion of regular human insulin is the treatment of choice

RSSDI treatment algorithm recommends administration of an intravenous bolus dose of 0.1 U/kg, followed by continuous intravenous infusion of insulin at the rate obtained by dividing the current blood glucose value with a factor of 100. The necessity of the initial bolus has been called into question by one study that demonstrated no differences in outcomes or hypoglycemia risk among a group of 157 patients who either did or did not receive an initial insulin bolus. Several studies have shown that insulin administration and force hydration result in a fairly predictable decrease in plasma glucose concentration at a rate of 65–125 mg/dL/h. The insulin rate should be decreased to 0.05 U/kg/h and dextrose should be added to the intravenous fluids when the plasma glucose concentration reaches ~ 11.1–13.9 mmol/L. The insulin infusion rate should be adjusted to maintain a plasma glucose level of 8.3–11.1 mmol/L until ketoacidosis is resolved, as indicated by normalization of venous pH and anion gap. Insulin infusion should be continued among patients with hyperosmolar hyperglycemic state (HHS) until mental obtundation and the hyperosmolar state are corrected [249].

The use of subcutaneous rapid-acting insulin analogs (lispro or aspart), administered every 1–2 h, is as effective as the use of intravenous regular human insulin among patients with uncomplicated mild to moderate DKA. After an initial bolus subcutaneous dose of 0.2–0.3 U/kg, the administration of lispro or aspart (subcutaneous doses of 0.1 U/kg/h or 0.2 U/kg/2 h) causes similar reduction in glucose concentration as that achieved using the intravenous route. Once glucose levels reach ~ 250 mg/dL, the dose of subcutaneous insulin should be reduced by half and should be continued intermittently until DKA resolves. Administration of insulin intramuscularly is also been found effective in the management of DKA; however, this route tends to be more painful than subcutaneous injection and might increase the risk of bleeding among patients receiving anticoagulation therapy. The use of rapid-acting subcutaneous insulin analogs is not recommended for patients with severe hypotension or those with severe DKA or HHS. Until now, none of the prospective randomized studies have compared the subcutaneous infusion of rapid-acting insulin analogs with the intravenous infusion of regular human insulin among patients admitted to the ICU [249].

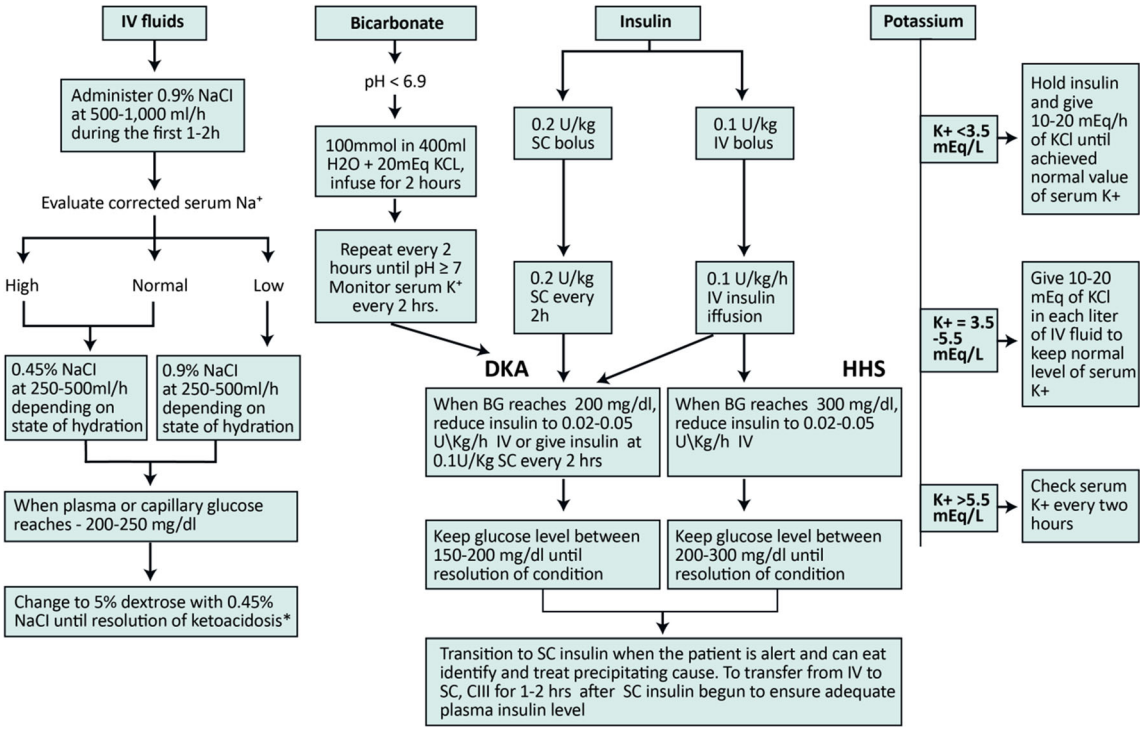

Fig. 15 Protocol for management of DKA and HHS. KCL, potassium chloride; SC, subcutaneous; IV, intravenous; DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state; BG, blood glucose; NaCl, sodium chloride; mEq/L, milliequivalents per liter

Recommendations from RSSDI for patients with DKA and HHS

- Protocol for management of DKA or HHS: fluid resuscitation, avoidance of hypokalemia, insulin administration, avoidance of rapidly falling serum osmolality, and search for precipitating cause
- Short-acting intravenous insulin infusion of 0.10 units/kg/h should be used in adults with DKA.
- The insulin infusion rate should be maintained until the resolution of ketosis occurs which can be measured by normalization of the plasma anion gap and venous pH.
- Intravenous dextrose should be started when plasma glucose concentration falls to14.0 mmol/L in order to avoid hypoglycemia.

Barriers and myths concerning insulin

Although most PCPs believe that the initiation of insulin therapy is an essential component in the management of T2DM, many still consider it to be the "last option" and indicate that their patients are reluctant to accept this therapy [250]. In the seminal Diabetes Attitudes, Wishes, and Needs (DAWN) study, Peyrot et al. reported that approximately 50% of healthcare professionals delay insulin initiation until it is "absolutely necessary" [251]. Similarly, the SOLVE™ (Study of Once Daily Levemir), a multicenter observational study that involved over 17,374 patients with T2DM in 10 countries (Europe, Asia, and North America), showed that insulin initiation is generally delayed until an average HbA1c level of approximately 9% [252]. Several other studies across many countries have confirmed that there is significant delay in the initiation of insulin therapy. This reluctance to initiate insulin treatment may be related to patient, provider, or system factors (Table 14) [250]. Summary of the articles evaluated the barriers is shown in Table 15 [253–256].

Table 14 Barriers and myths concerning insulin

Patient barriers	Provider barriers	System barriers
Fear of injection and needle	Anxiety, fear and pain reducing strategy	Limited access to education
Psychological resistance	Monitoring of therapy	Limited training of providers in injection technique
Fear of weight gain	Fear of weight gain	Overburdened workload among providers
Socioeconomic status	Fear of hypoglycemia	Poor adherence
	Patient's adherence, and wish to prolong non-insulin therapy	

Table 15 Summary of the articles evaluated the barriers

Ref.	Design	Study aims	Sample and setting	Tools and outcome measures	Results and conclusions
Raj et al. (2018)	Open-label, multicentric, real-world data	To understand the barriers and behaviors of insulin therapy among T2DM pts in India from a real-world setting	3192 (30.6%) pts receiving insulin therapy have moved on to various therapies observed over 9 months	Data analysis of 3192 pts to understand the reasons for shift in therapy	Barriers for initiating insulin therapies were hypoglycemic episodes (25.9%), stress (17.1%), fear of injection (10.3%), and cost (7.4%) Education and empowerment (stress, fear of injection and cost) through shared decision-making allow patients' preferences to be presented
Alberti et al. (2002)	Cross-sectional	To identify a broad set of attitudes, wishes, and needs among both people with diabetes and care providers	5104 pts with T2DM and diabetes care providers (nurses = 1122; physicians = 2705)	Questionnaire-based survey	Patients on insulin therapy in India expressed concern over hypoglycemia (25–55%) and weight gain (40%) Strategy to bridge the barrier • Raise awareness and advocacy • Educate and mobilize people with diabetes and those at risk • Train healthcare providers and enhance their competencies • Provide practical tools and systems. • Drive policy and healthcare systems change.
Patel et al. (2012)	Qualitative	To identify healthcare professionals' perspectives on delaying insulin initiation for T2DM patients in a multi-ethnic setting	14 healthcare professionals (general practitioners, specialists and nurses) Conducted in the UK	Semi-structured, face-to-face, interviews	Barriers for initiating insulin therapy for South Asian diabetic patients could be over-accentuated by the presence of language barrier and the lack of patients' understanding about the disease and its therapy. South Asian patients seem to be more likely to be negatively influenced by observations and experiences about insulin treatment within their community
Lakkis et al. (2013)	Cross-sectional	To investigate family physicians' attitudes towards insulin therapy in T2DM patients in Middle Eastern Arab countries	122 family physicians Conducted in Middle Eastern Arab countries	Online questionnaire-based survey	73.6% of family physicians chosen to delay insulin initiation until it is absolutely necessary 64% of family physicians reported hesitancy to start insulin mostly due to apparent patient reluctance

Recommendations from RSSDI for barriers and myths concerning insulin

- Education is considered the cornerstone of interventions to address both clinician and patient barriers regarding initiation and intensification of insulin therapy.
- Need to encourage clinicians to establish and foster strong relationship with diabetes educators who have the knowledge, skills, and potential to support their patients during intensification of insulin therapy.
- Diabetes educator and clinicians should focus on the availability of long- and short-acting analogs and premixed formulations when possible, insulin delivery devices, weight gain and other side effects, dose flexibility, and cost.
- Use of pen devices is widely accepted and is associated with greater persistence and improvement in patient outcome.
- To provide education to patients and family members/caregivers is an ongoing need, beginning with conversations before initiation, at the time of initiation, and when dose intensification of insulin is required.

Biosimilar insulins

Biosimilar is a protein molecule which is a duplicate copy of already existing insulins having an identical amino acid sequence (not withstanding minor variations in clinically active components) and with no significant differences in efficacy and safety. European Union guidelines have stated that for manufacturing biosimilar insulins, their safety and efficacy profile should be similar to those of the *original* insulin formulation [44]. In 2018, a systematic review was carried out which compared Basalog, LY2963016, Basalin, and MK-1293 with Lantus while SAR342434 with Humalog with respect to their efficacy and safety [257]. Various clinical studies suggested similar clinical efficacy, immunogenicity and adverse events.

Recent examples of biosimilar insulin development are summarized in Table 16.

Recommendations from RSSDI for biosimilar insulins

- Dose titration should be advised before switching from original insulin to biosimilar insulin starting with a reduced dose and to up-titrate to avoid hypoglycemia.

Smart insulins

The "smart" (glucose-responsive) insulins are those who deliver insulin according to an endogenous glucose-sensing feedback mechanism [258]. The classification of "smart" insulins are shown in Table 17 [258].

Development of non-injectable insulin products

Inhaled insulin

Technosphere insulin (TI) is an alternative to subcutaneous prandial insulin which is delivered in a compact handheld inhaler device and has been approved in the USA by the Food and Drug Administration (FDA) for the treatment of individuals with T1DM and T2DM [259].

Inhaled insulin is available in the form of a freeze-dried powder of recombinant human insulin adsorbed onto fumaryl diketopiperazine and form microparticles for inhalation. It has a limited duration of action which lasts for approximately 2–3 h during which it rapidly gets absorbed within 12–15 min of inhalation with a peak action of approximately 53 min. The action profile of TI is similar to that of rapid-acting insulin [260].

A breath-powered device is used for the delivery of technosphere insulin which converts the powder formulation into lightweight particles and causes dispersion. The drug completely gets cleared from the lungs after 12 h of absorption. Clinical evidences in individuals with T2DM, CV safety outcomes, and long-term surveillance are required [259]. Afrezza, an inhaled form of rapid-acting insulin developed by using a technosphere technology, has been approved by the FDA in 2014. This insulin has safer PK profile in comparison with previously failed inhaled form of insulin (Mohanty, 2017: 28571200).

Table 16 Various human insulin and analogue insulin sold in India

Human insulins	Analog insulin (glargine)
Insugen R, 30/70,50/50, N (Biocon)	Basalog (Biocon; India launch year: 2009)
Humstard 30/70 (Zydus)	Basugine (Lupin (Synox); India launch year: 2013)
Humarap (Abbott, Cadila)	Glaritus (Wockhardt; India launch year: 2009)
Lupisulin-R, M30, M50, N (Lupin: India)	Basaglar (Eli Lilly/Cipla; India launch year: 2018)
Recosulin-R, 30/70, 50/50, N (Shreya Life Sciences: India)	
Human Fastact (Eli Lilly *an*d Company: India)	
Mixact 30/70 (Novo Nordisk)	
USV discontinued Wosulin R, 30/70, 50/50, N (Wockhardt; India launch year: 2003)	

Table 17 Classification of "smart" insulins

Types	Mechanism
Conventional	
Protein-binding ligand (lectin)	• Concavalin A was used to bind to glycosylated insulin, which retained its bioactivity • This insulin ligand complex released insulin upon being stimulated by ambient hyperglycemia to dissociate
Bulk hydrogel matrix	• Used glucose oxidase as a glucose-sensing mechanism • Glucose oxidase swell in response to hyperglycemia • This stimulates entrapped glucose to break down and activate insulin
Phenyl boronic acid	• Glucose-sensitive self-regulated insulin delivery
Nanotechnology-based smart insulins	
Nano-membranes	• Release of insulin depends on glycemic levels
Microgel (smart sponge)	• Regulated insulin release in response to ambient glycemia
Nano-network	• Glucose-mediated insulin delivery

Oral insulin

The most common route for insulin administration has been the subcutaneous route, but in the last few years, efforts have been made to change the route of administration from subcutaneous to an oral route [261].

There are several barriers such as physical barrier, the enzymatic barrier, and the instability of insulin in the gastrointestinal tract for the oral administration of insulin. But recent studies have summarized various nanotechnology-based strategies for the development of insulin delivery by the oral route [262].

Apart from being a non-injectable route of administration, oral insulin also depicts physiological insulin extraction as it directly enters the portal circulation and promotes increased uptake of net hepatic glucose production [262, 263].

Oral insulin replicates the exact secretion of exogenous insulin from the pancreas. After getting absorbed by the intestinal walls, it reaches in higher concentration into the liver through the portal vein.

Oral insulin has number of barriers which can be mainly of three types:

- Physical barriers
- Biochemical barriers
- Formulation barriers

The various strategies that have been suggested in the various studies include:

- Chemical modification
- Targeting receptor/tissue
- Formulation technologies

Initiation of some innovative approaches such as mucoadhesive polymers, absorption enhancers, protease inhibitors, and particulate carrier systems has boosted the scope of research in delivering insulin orally by counteracting the naturally existing hurdles and harsh conditions of the GIT. Funding, on the other hand, has always been a paramount limitation to obtain thorough PK and pharmacodynamic data in animals and humans and possible long-term side effects of the newly introduced oral insulin candidates [262, 263].

Buccal insulin

In the past few years, buccal mucosa has been found to be a promising delivery route for administration of insulin as it has a rich vasculature, immobile mucosa, and anexpanse of smooth muscle [264].

The various advantages of using buccal mucosa for the administration of insulin include:

- Avoids presystemic metabolism of insulin
- Protects stomach from the direct contact of acid labile insulin
- Less enzymatic activity
- Improves patient compliance as it eliminates the pain caused by injections

Oral-lyn (Generex Biotechnology Corporation, Toronto, Canada) is currently the only buccal insulin available which can be administered along with food and is licensed for use in countries such as Southeast Asia, Africa, and South America. It is also currently enrolled in an FDA-approved Investigational New Drug Treatment program with a phase III trial planned [264, 265].

Oral-lyn is a proprietary liquid formulation of human recombinant insulin which can be administered through a spray device. This spray device delivers aerosol at high velocity (~ 100 mph) and is further absorbed by the mucosal lining of the oral cavity. Each puff delivered is equivalent to 1 unit of insulin absorbed into the systemic circulation [264, 265].

As it is absorbed quickly from the vascular oral mucosa, a decrease in the glucose activity can be seen within 5 min, showing a peak insulin action at around 30 min, and a duration of action is of 2 h (shorter than subcutaneous human insulin) [264, 265].

It has been seen that glycemic efficacy of both Oral-lyn and regular human insulin is comparable in individuals with T1DM receiving twice-daily basal insulin analog [266]. It was observed that when Oral-lyn was added to oral glucose-lowering agents in individuals with T2DM with inadequate glycemic control, there was a great reduction in postprandial glucose levels within 2 h as compared with oral glucose-lowering agents. Comparative studies with insulin analogs in T2DM have not yet been carried out.

Occasional mild, self-limiting dizziness is some of the side effects observed in some of the clinical studies. Insulin spray formulation may significantly impact treatment compliance [267]. However, more clinical studies are needed to inform glycemic durability, safety, and tolerability.

Conclusion

Insulin has been the most effective and durable hypoglycemic agent for the management of diabetes. Early treatment intensification with insulin in those who fail to achieve glycemic goals is important for reducing complications in the Indian population with wide ethno-geographic differences. We hope that adoption of these consensus recommendations will simplify the understanding of insulin therapy among clinicians and help better healthcare delivery to people with diabetes.

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