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Review article

Insulin analogs: Glimpse on contemporary facts and future prospective

Arun K. Sharma[a,*], Gaurav Taneja[b], Ashish Kumar[c], Megha Sahu[d], Gunjan Sharma[d], Asim Kumar[a], Satish Sardana[a], Aakash Deep[e]

[a] Department of Pharmacology, Amity Institute of Pharmacy, Amity University, Gurugram, Haryana 122051, India
[b] Fortis Healthcare Limited, UBP, 4rd Floor, Sector 41, Gurugram, Haryana 22001, India
[c] Department of Pharmaceutics, Amity University, Noida, Uttar Pradesh 201303, India
[d] Department of Pharmacology, Amity University, Noida, Uttar Pradesh 201303, India
[e] Department of Pharmaceutical Chemistry, Chaudhary Bansi Lal University, Bhiwani, Haryana 127021, India

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ABSTRACT

Insulin remains a predominant life-saving medication for type 1 and type 2 Diabetes Mellites. Natural insulin secretion limits the fluctuation of the narrow and high surge of blood glucose levels. However, imitating the same by external insulin remains a challenge as a variety of insulin analogs (rapid acting, short acting, intermediate acting and long-acting) have different pharmacokinetic (PK) and pharmacodynamic (PD) properties. Inconsistent reduction in overall hyperglycemia level and nocturnal hypoglycemia due to variable absorption time and time action profile predominantly highlights the need of revisiting the PK/PD of insulin analogs as single analog is not yet sufficed to replace internal insulin exogenously. Combination therapy with basal and prandial insulins or intensification of hypoglycemic therapy with premixed insulins are of prime importance in managing diabetes effectively, imitating the natural insulin secretion. Therefore, the knowledge of PK/PD properties might help a practitioner to design, implement and manage insulin replacement therapy effectively and averting adverse events. Present study reports the comparative analysis of PK/PD profile of various insulin analogs based on the concurrent information about clinical aspects. Moreover, study interlinks the major concerns of therapeutic efficacy of insulin analogs with their respective onset of action and duration of effectiveness and reported adverse drug reaction which explore the scope of improvement.

1. Introduction

Diabetes Mellitus is a metabolic disorder characterized by elevated level of blood glucose either due to insulin deficiency or increased insulin insensitivity. Statistical measurements of the International Diabetes Federation (IDF) revealed about 8.3% increased prevalence of diabetes mellitus worldwide which directly reflects the vulnerability of around 425 million people [1,2]. Diabetes Mellitus attributes about 8.2% mortality in total deaths throughout the globe by the year 2011 [3]. CDC reports noticed the diabetic disorder as the seventh leading cause of mortality and third most common pathological state in North America (Fig. 1). Indeed, half of the diabetic population is not even aware of having the disease which twice the risk of various associated complications. Although, 90% diabetic patient are reported with type 2 diabetes mellitus (T2DM) and rest with type 1 diabetes mellitus (T1DM) or juvenile diabetes characterized by complete loss of endogenous insulin production due to autoimmune destruction of β cells [4,5], but the grievousness of T1DM is more due to association of constant high level of ketoacidosis. The exact molecular aspects of pathological events for T1DM is still unknown but, it is attributed to environmental and genetic predisposal of an individual [6]. Despite the fact that, T2DM initially started with the loss of insulin sensitivity and eventually progressed to functional impairment of β cells but also require insulin treatment [7,8]. Diabetes Mellitus is not only the self-destructive disorder but also provokes various pathological signalling that ultimately cause fatal complications (Fig. 1). Conversely, exogenous insulin is the only treatment for T1DM patients which signify the importance of insulin and its analogs.

Secretion of natural insulin is based on the sustainability of basal glucose levels within a narrow range for the steady and slow release of insulin between meals and regulation of post-prandial glucose for rapidly surging insulin in response to meals ingested [9]. Normal subcutaneous insulin therapy reproduces the physiological action of natural insulin but fails to mimic the rhythmic secretion of the pancreas in response to blood glucose levels. Insulin analogs are prepared synthetically with a small amino acid change in sequence to achieve desirable

* Corresponding author at: Department of Pharmacology, Amity Institute of Pharmacy, Amity University, Gurugram, Haryana 122051, India.
E-mail address: akumar10@ggn.amity.edu (A.K. Sharma).

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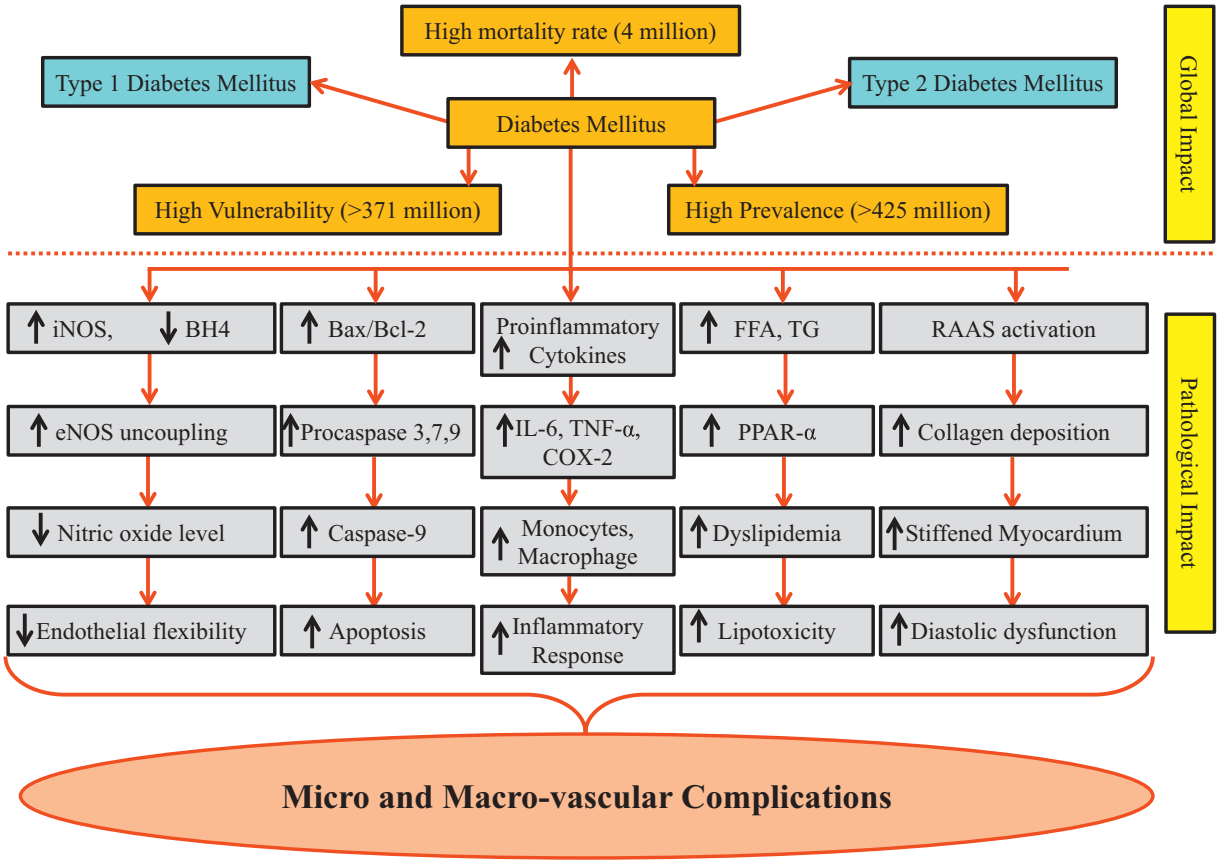

Fig. 1. Schematics of global and pathological impact of diabetes mellitus. iNOS, Inducible nitric oxide synthase; BH4, Tetrahydrobiopterin; eNOS, Endothelial nitric oxide synthase; Bax, Bcl-2-associated X-protein; IL-6, Interleukin 6; TNFα, Tumor necrosis factor alpha; COX-2, Cyclooxygenase-2; FFA, Free fatty acids; TG, Triglycerides; PPAR-α, Peroxisome proliferator-activated receptor alpha; RAAS, Renin angiotensin aldosterone system.

PK. Soluble human insulin acts as a hexamer at the site of injection which is too slow to get absorbed from the site of injection and fails to address the post-prandial surge of plasma glucose. Intermediate-acting insulin demonstrates the trailing-off effect preceding after an inappreciable peak effect. Moreover, long-acting insulin provides a flat time-action profile with an extended duration of action with a single dose [10,11]. In addition, rapid and ultra-long-acting insulin analogs have also been developed. Premixed insulin analogs are a mixture of rapid and slow acting insulin in various proportions to mimic both basal and prandial effect of insulin secretion phases in a single shot. In order to achieve the desired effect as of natural insulin, one must have detailed about PK and pharmacodynamic (PD) attributes of insulin analog. Therefore, the present literature review hereby aims to explain the PK and PD properties of various insulin analogs with their prospectus to plasma glucose maintenance.

2. Insulin and insulin analogs

Replacement therapy mainly focuses to replicate the endogenous secretion of insulin in a similar pattern of basal release from the pancreas (small regulation and prandial release or excursion postprandial). Therefore, insulin replacement therapies comprised of basal insulin and bolus insulin dose. Insulin analogs are classified as rapid, short, intermediate and long-acting products based on their PK properties. Rapid and short-acting insulin analogs have been used as bolus doses and intermediate and long-acting products have been used as basal doses (Fig. 2). A detailed PK classification has been depicted in Table 1 based on onset of action, peak plasma concentration and duration of action.

3. Basal insulins (intermediate and long-acting insulins)

Intermediate-acting insulin (Neutral Protamine Hagedorn, NPH) and long-acting insulin (glargine, detemir) are the basal insulin analogs currently used in clinical scenario. Recently, insulin degludec has also been approved in some countries (Fig. 3) [12]. Even, basal insulin analogs provide with an equivalent glycemic control, lower risk of hypoglycemia as compared to NPH insulin [13–15] but only a limited proportion of patients achieved the glycemic control to meet current clinical guidelines. Therefore, it creates a need for further improvement in this area. The injected insulin shows a different PK feature as compared to endogenous insulin secretion where the steady release of basal insulin gets amplified to provide peak levels in response to a meal. A subcutaneous injection of insulin demonstrates a peak followed by trailing-off. Therefore, the PK profile of basal insulins are protracted but this might be still an approximation to the steady and smooth profile of healthy endogenous basal insulin release which increases the risk of hyperglycemia when insulin levels become too low and vice versa [16]. Some tactics have been used for the protraction of insulin analogs including NPH insulin that includes protamine zinc complex which reduces its solubility [17] and extends the release for the intermediate duration of action (12–18 h with peak effect at around 4 h) [18]. The major disadvantage with NPH is the requirement of re-suspension before injection which invariably causes inconsistent dosing [18]. 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 shifting the isoelectric point making it less soluble at physiological pH [19,20]. Deletion of threonine at position B30 with an addition of myristic acid to lysine at

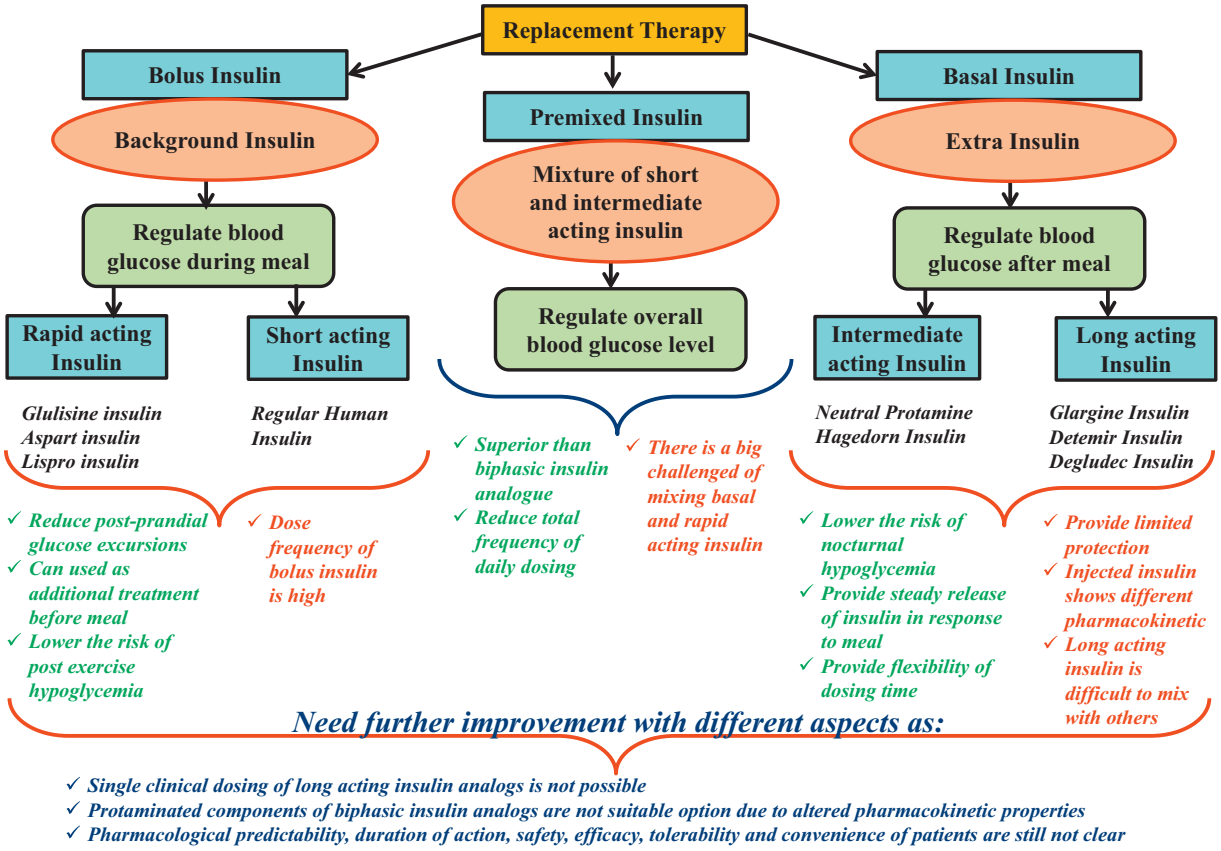

Fig. 2. Figure illustrates the different kind of insulin analogs with their positive and negative aspects.

B29 has developed insulin detemir. These changes increased the hexamer stability and promoted dihexamerization which in-turn protracted the absorption of insulin detemir at the injection site. Moreover, it also aided reversible binding to albumin in subcutaneous tissue as well as in circulation. The deletion of threonine at position B30 and addition of 16-carbon fatty acid side chain to lysine at B29 via γ-L-glutamic acid linker developed dihexamersinsulin degludec. Insulin degludec formulation is stabilized as dihexamers with phenol and added zinc whereas, on administration phenol has rapidly eliminated and dihexamers formed large multi-hexamers which gradually released into

Table 1
Pharmacokinetic, Pharmacodynamic and structural properties of insulin and its analogues.

Insulin analogs	Alteration	Onset of action	Peak action time	Duration of action
Short acting				
Regular [64]		~30 min	1.5–3.5 h	7–8 h
Rapid acting insulin				
Lispro (Humalog) [65]	Reversal of amino acid proline at B28 and lysine at B29	~15 min	30–70 min	2–5 h
Aspart (Novorapid) [66]	Replacing proline at B 28 with aspartic acid	10–20 min	1–3 h	3–5 h
Glulisine (Apidra) [67]	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 (Humulin-N) [68]	Neutral protaminated insulin	1.5–4 h	2.8–13 h	Up to 24 h
Long acting				
Glargine (lantus) [69]	Asparagine replaced with glycine at A21 and two arginine amino acids added at position B31 and B32	1–3 h	No peak	Up to 24 h
Detemir (Levemir) [70]	Myristic acid acylation to the lysine residue on position B-29 and Deletion of threonine from B30	1–2 h	6–8 h	Up to 24 h
Deludec (Tresiba) [71]	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 Humulin 70/30 [72]	70% Isophane insulin and 30% Regular insulin	30–90 min	1.5–6.5 h	18–24 h
Premixed insulin analogues				
ProLispro/Lispro Humalog 75/25 [73]	75% neutral protaminated insulin lispro and 25% insulin lispro	10–30 min	0.5–4 h	Up to 24 h
ProLispro/Lispro Humalog 50/50 [74]	50% neutral protaminated insulin lispro and 50% insulin lispro	10–30 min	0.75–2 h	Up to 24 h
ProAspart/Aspart NovoMix 70/30 [75]	70% protaminated insulin aspart and 30% insulin aspart	10–20 min	1–4 h	Up to 24 h

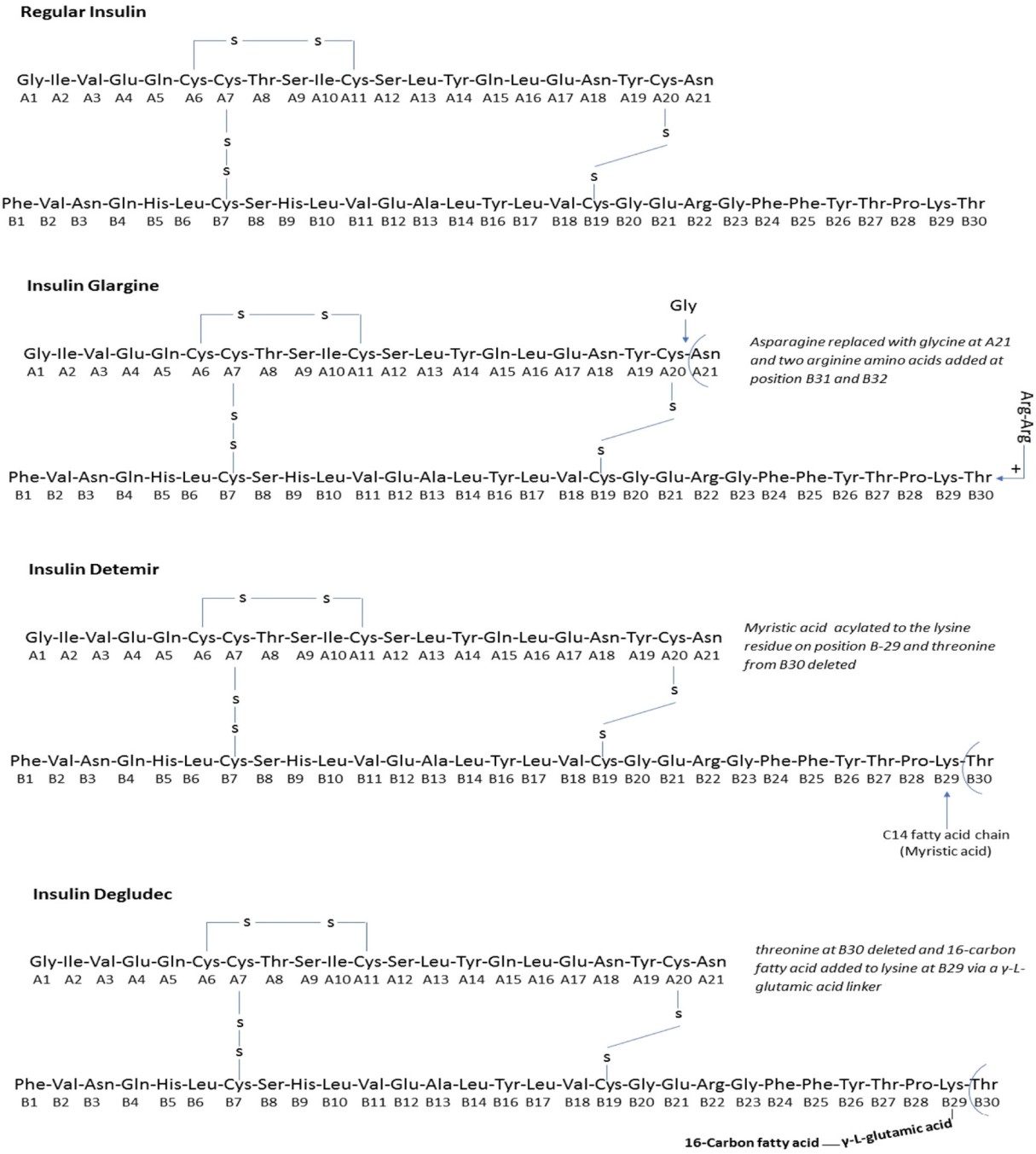

Fig. 3. Structural arrangement of basal insulin analogs.

circulation in form of monomer and zinc slowly diffused away from the depot [21].

4. PK and PD summary of specific analogs of basal insulins

4.1. Insulin glargine

Insulin glargine 100 U/mL (Gla-100, Lantus; Sanofi, Paris, France), was first approved in 2000. This analog has shown a significant incidence of lower nocturnal hypoglycemia as compared to NPH due to improved time action profiles. In order to obtain the PK and PD profile of insulin glargine, single-centric double-blinded study involving 34 patients with single subcutaneous dose of 0.8 U/kg glargine was conducted and the PK data thus obtained showed that insulin glargine possessed Cmax 26 pmol/L, tmax 540 min, AUC (0–last) 81,100 pmol·min/L and AUC (0–∞) 144,000 pmol·min/L respectively. Similarly, the PD data obtained through Euglycemic Clamp Techniques showed insulin glargine possessing release time (tRlast) up to 1430 min when total amount of infused glucose (Gtot) was 1250 mg/kg, maximum glucose infusion rate (Rmax) was 1.68 mg/min/kg, time to maximum glucose infusion rate (tRmax) was 6.13 min and value of last measurable glucose infusion (GIRlast) was 0.366 mg/min/kg [22]. The development of new long-acting insulin analogs has provided improved flexibility of dosing time, simplified insulin dose titration and better glycemic control in people with T1DM or T2DM. Insulin Glargine U300 (Gla-300) is another long-acting insulin analog with similar molecular structure, mode of protraction and metabolism as Gla-100 [23]. Some studies have reported the comparison of both glargine formulations but

the PK and PD estimation of Gla-300 suggested the flatter and more prolonged glycemic control in T1DM as compared to Gla-100 (33 h vs. 29 h) [23,24]. It has been found that peak concentrations achieved by Gla-300 were lower but the improved PK profile resulted in an even distribution of glucose-lowering effect across 24 h period with reduced variability in glucose lowering in defined time format and between days of the study. Although, phase III clinical trials have reported the good safety, well tolerability and similar glycemic control of Gla-300, a lower rate of hypoglycemic events, particularly nocturnal episodes were observed as compared to Gla-100 [25]. Similar findings were reported by Hurren et al. that revealed constant, evenly distributed and prolonged PK and PD profile of Gla-300 at steady state but with less potency [24]. Gla-300 has prolonged duration of action and provide a continuous 24 h release to the patient with a single administration in contrast to Gla-100 where twice dose is required per day. There are two different commercially available glargine derivatives namely LY2963016 (LY IGlar) and Lantus (IGlar) which are produced by different techniques but contain the identical amino acid sequence. A randomized, double-blind, single dose, two periods, crossover study carried with 221 subjects reported both the derivatives possessing similar duration of action and PK/PD properties under a given dose of 0.5 units/kg s.c [26]. Meta-analysis of 16 trials including Asian and non-Asian participants revealed the effective potential of Gla-100 in lowering HbA1c and fasting plasma glucose (FPG) in Asians with T2DM. Furthermore, the consequence showed the similar incidences of hypoglycemia in both populations whereas, a less absolute weight gain in Asians as compared to non-Asians [27]. The recent study demonstrated the low variability in glucose lowering and more evenly distributed pharmacokinetic profiles of insulin glargine (Gla-300) as compared to Deg-100 at a dose of 0.4 U/kg/day single morning dosing regimen [28]. It is intriguing to note that elder patients with T2DM treated with Gla-300 have been found to have more glycemic control, lesser incidences of hypoglycemia and lesser weight gain as compared to Gla-100, authors thereby suggest that Gla-300 might be a wise choice for treating T2DM in elder patients [29,30].

4.2. Insulin detemir

Insulin detemir (Levemir® by Novo Nordisk) is another long-acting basal insulin analog which forms an irreversible bond with albumin and upsurges its systemic absorption. Detemir and glargine, both have the capability to produce lower but reproducible peaks and sustained release as compared to other intermediate and long-acting analogs. The key significant difference of detemir is to produce less intrasubject variability due to metabolic inconsistency and as well as lower risk of hypoglycemia. PK/PD profile was measured by a single center via a double-blinded study involving 34 patients and received a single subcutaneous dose of detemir (0.8 U/kg). PK data revealed the parameters including Cmax 7680 pmol/L, tmax 540 min, AUC (0–last) 6,500,000 pmol·min/L and AUC (0–∞) 8,030,000 pmol·min/L respectively. Whereas, the PD data has been obtained from Euglycemic Clamp Technique which depicted the tRlast up to 1.57 (min), Gtot 1.45 mg/kg, Rmax 47.8 mg/min/kg, tRmax 126 min and GIRlast 1.22 mg/min/kg respectively [22]. Randomized, double-blinded, crossover study with 24 T1DM subjects was carried by Porcellati et al., 2007 which also confirm the flatter and longer duration of action of insulin detemir with low intrasubject variability and fluctuations as compared to NPH. In addition, PK/PD data of insulin detemir also suggested a lower risk of nocturnal hypoglycemia in T1DM patients in contrast to NPH [31]. A recent study reported no statistical difference in hypoglycemic events with insulin detemir as compared to insulin glargine but glargine showed more significant glycemic control over insulin detemir on the 7th day of treatment. But the authors suggested these low hypoglycemic events last till 7th day of treatment which is not clinically significant [32]. Furthermore, another safety study suggested a lower risk of hypoglycemia with insulin detemir as compared to insulin glargine and NPH insulin. The hazard ratio for insulin glargine and insulin detemir was found to be 0.92 and 0.70 respectively with reference to NPH insulin [33].

4.3. Insulin degludec

Insulin degludec (IDeg) is another basal insulin having ultra-long duration of action with stable glucose lowering effect and reduced intra-individual variability resulting in 24 h consistent basal insulin coverage by a single dose administration. It has a distinct absorption mechanism including a formation of multi-hexamers in subcutaneous tissue after dose administration which further releases numerous IDeg monomers. Some PK/PD investigation reported that IDeg has a half-life of more than 25 h and reaches steady state within 3 days of administration [34]. The PK profile of IDeg in blood samples containing IDeg (0.4 U/kg) demonstrated an even distribution of exposure across one dosing interval AUC (0 − 12 h) with total area under the curve from 0 to 12 h at steady state in % (SS/AUCτ,SS) and total area under the curve over a 24 h dosing interval at steady state in % (AUCF%τ,SS) 53% and 14% respectively. The PD profile of IDeg obtained by euglycaemic clamp technique report a stable and even distribution of glucose-lowering effect across all four 6 h intervals in 24 h period with area under the curve of glucose infusion rate(AUCGIR) for 0–12 h, total area under the curve of glucose infusion rate from 0 to 12 h at steady state in % (SS/AUCGIR,τ,SS) and total area under the curve of glucose infusion rate over a 24 h dosing interval at steady state (AUCFGIR,τ,SS) 51% and 0.25 (mg/kg·min) respectively in a given dose of 0.4 U/kg [35]. Further, the study conducted by Ikushima et al. evaluated the consistent steady-state distribution for a mean of 24 h effect of degludec in Japanese patients. The mean AUCGIR (0–12 h), SS/AUCGIR,τ, SS was found 48%, suggesting that the glucose-lowering effect of IDeg was relatively uniformly distributed across the first and second 12 h of the 24 h dosing interval [36]. Moreover, Hompesch et al. reported the PK/PD responses of IDeg in 3 ethnic groups of patients with T2DM which observed the flat, stable, long- and uniform-time distribution to achieve clinical steady state in all subjects from different racial or ethnic backgrounds, including Japanese subjects with T1DM and African American, Caucasian and Hispanic/Latino subjects with T2DM [37]. IDeg is available in two forms 100 U/mL (U100) and 200 U/mL (U200). A double-blind, crossover, randomized study under steady-state conditions with T1DM revealed that IDeg U100 and IDeg U200 were bioequivalent and the glucose-lowering effect at steady state was comparable between both formulations [38]. Clinical evidence from Phase 3 clinical trial also suggested that IDeg provides an effective glycaemic control which is quite similar to IGlar, but have decreased rates of hypoglycemia particular in nocturnal hypoglycemia. Studies also suggested lower within-day and day to day glycemic variability with IDeg than IGlar-U100 and IGlar-U300 [39]. A recent study suggested that daily single administration of IDeg lowered glycemic fluctuations than twice daily administration of IDet. It was observed that IDeg stabilized the plasma glucose level better during both day/night time and particularly before -and after breakfast with a relatively lower insulin dose than IDet [40].

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

Human insulin produced slower onset of action with a longer duration of action comparable to endogenous insulin surge [41]. The rapid-acting insulin was developed with an intent to fasten insulin absorption thereby minimizing post-prandial glucose excursions effectively. Three rapid-acting insulin analogs have been so far developed namely insulin lispro, insulin aspart, and insulin glulisine (Fig. 4). These analogs can be used as an additional treatment (before meals) with basal therapy to mimic the endogenous insulin surge post-prandially [42] or to supplement the oral hypoglycemic agents. All the rapid-acting insulin analogs were developed by making changes in

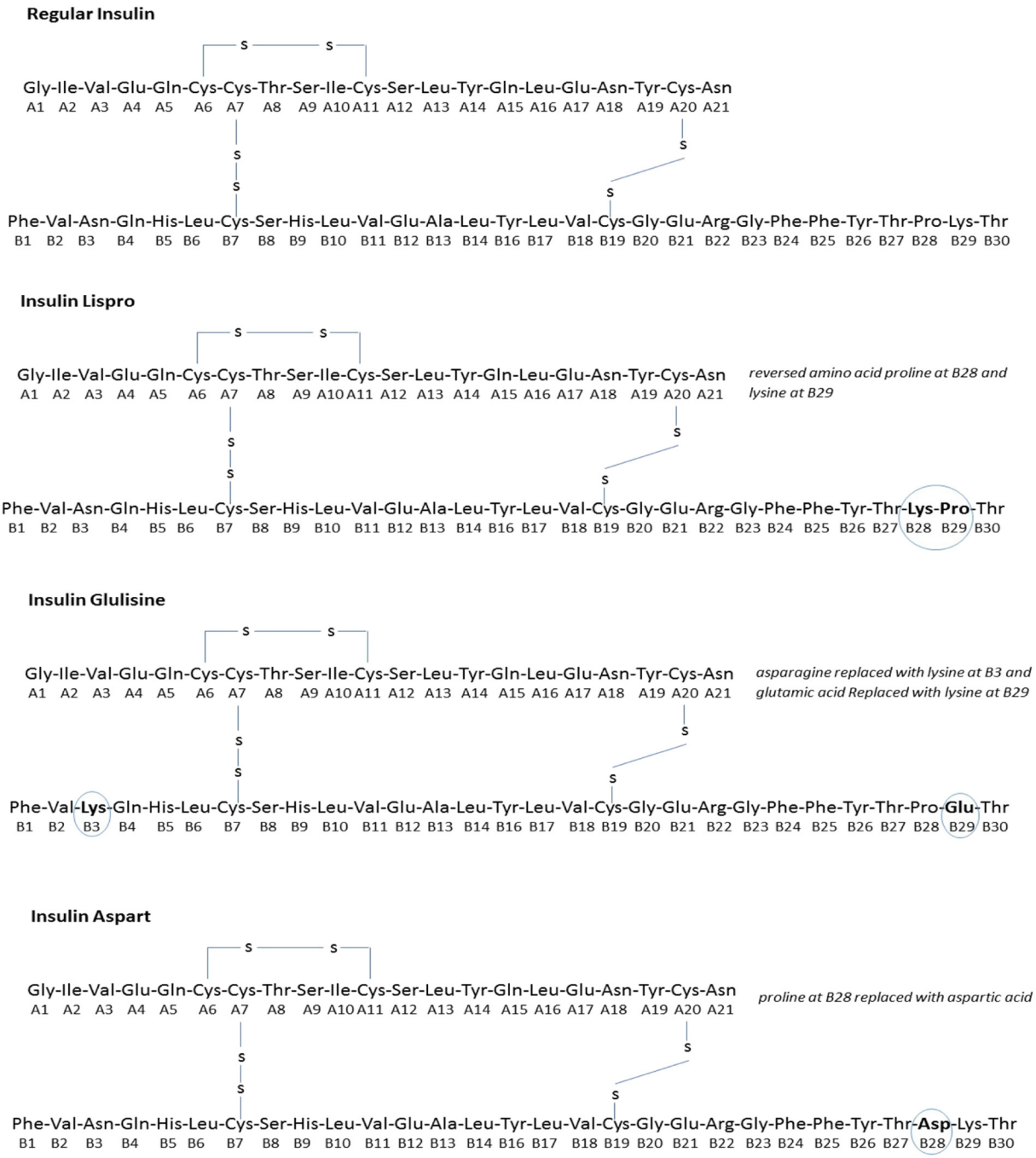

Fig. 4. Structural arrangement of bolus insulin analogs.

amino acid sequences for an instance replacement of proline by lysine at B28 and lysine by proline at B29 leads to the development of insulin lispro. Whereas, insulin glulisine was developed by replacing asparagine with lysine at B3 and replacing of lysine with glutamic acid at B29. In addition, insulin aspart has been designed by replacing proline by aspartic acid at B28. These changes in B-chain of insulin impaired the tendency of insulin chains to aggregate as dimers and hexamers, hence monomeric form absorbed more rapidly into circulation after subcutaneous injection [43,44].

6. PK and PD summary of specific analogs of bolus insulins

6.1. Insulin lispro

The PK aspects of insulin lispro demonstrated based on the glucose clamp technique by involving eight non-diabetic individuals with estimation of absorption and activity profiles of Lispro after subcutaneous injection of 0.4 U/kg in a randomized crossover fashion [45]. The Cmax and Tmax of insulin lispro was reported to be 2.02 ± 0.69 and 371 ± 185 respectively with area under curve of mean serum immune reactive insulin versus time determined from 0 to 15 h (AUC15) was 1092 ± 327 ng·min/mL and area under the curve of mean serum immunoreactive insulin versus time determined from 0 to a return to baseline value (AUCt') were found to be 966 ± 447 ng·min/mL. PK

study based on glucose clamp technique defined the maximum glucose infusion rate (GIRmax), time to achieve GIRmax (tGIRmax), and cumulative total amount of glucose infused during data collection (Gtot) as 3.69 ± 1.43 mg/min/kg, 268 ± 145 min and1.90 ± 0.71 g/kg respectively [45]. In order to estimate the activity of rapid-acting analogue with continuous subcutaneous insulin infusion (CSII), a study on 20 T1DM patients was conducted with lispro analogue using clamp technique for 24 h and findings revealed that the plasma insulin concentration of CSII was 20.6 ± 0.2 μU/mL between a time period of 4 and 24 h whereas plasma glucose levels were found to be 130 ± 2 mg/dL until for 24 h [46]. PD aspects revealed the onset of action, duration of action and end point of action which were 0.5 ± 0.1 h, 23.5 ± 0 h and 24 ± 0 h respectively with GIR 1.4 ± 0.4 mg/kg/min and plateau time 5–24 h. Insulin lispro protamine suspension (ILPS) in T2DM with a single dose of 0.8 U/kg showed the value of Cmax as 208 pmol/L and tmax as 540 min, whereas the value of AUC (0–∞) was found as 184,000 pmol·min/L. Moreover, the PD data revealed that the Gtot, GIRlast, and tRmax of ILPS were found as 2410 mg/kg, 0.253 mg/min/kg and 537 min respectively [22].

6.2. Insulin aspart

Tmax of insulin aspart has been found as 30.8 ± 13.8 which was significantly shorter as compared to human insulin for 0.025 U/kg, whereas Cmax of insulin aspart was 23.0 ± 6.0 which was markedly higher than human insulin [47]. Additionally, cumulative incremental curve against time (AUCt) for insulin aspart (1883 ± 410 μU min/mL) was also significantly greater than human insulin (1578 ± 270 μU min/mL) for 0.025 U/kg and (2439 ± 383 verse 3021 ± 405 respectively) for 0.05 U/kg. Similarly, for PD aspects insulin aspart induced a more profound and prompt response for lowering the plasma glucose level as compared to human insulin. Tmin of plasma glucose was significantly shorter for insulin aspart 51.3 ± 11.7 min than for human insulin 92.5 ± 34.3 on 0.025 U/kg and 69.6 ± 22.2 verse 124.2 ± 53.7 on 0.05 U/kg. The potential of glucose reduction (Cmin) was higher for insulin aspart 17.9 ± 6.8 mg/dL in comparison with human insulin 9.0 ± 2.5 on 0.025 U/kg and 26.6 ± 12.1 verse 17.3 ± 9.3 on 0.05 U/kg [47]. Moreover, the PK profile of insulin aspart for T2DM patients has demonstrated that the serum concentration of this analog was significantly increased after subcutaneous administration with therapeutic dose (0.11 ± 0.04 U/kg) whereas, mean Tmax was measured very fast (63 min) in comparison to Tmax value of endogenous insulin (84 min). Similarly, Cmax and AUC (0–180 min) values for insulin aspart were 391 ± 282 pmol/L and 42.8 ± 31.9 nmol min/L, respectively. Whereas, from PD point of view the administration of insulin aspart significantly attenuated postprandial hyperglycemia (Cmax and AUC (0–180) for glucose). The postprandial plasma glucose levels for 180 min were lower than plasma glucose levels before the meal as 6.1 ± 1.7 verse 7.7 ± 1.0 mmol/L, respectively. In addition, insulin aspart can significantly increase Tmax of glucagon up to 90 min as compared to non-diabetic individuals [48]. Moreover, to enhance the absorption of insulin aspart a new formulation containing niacinamide and L-arginine has been prepared. This fast-acting insulin aspart had demonstrated faster onset, higher early exposure and a potent early glucose-lowering effect as compared to conventional insulin as the part formulation in Japanese patients with T1DM [49]. Similarly, in the UK long-term effect of fast acting insulin aspart was accessed. The study projected that the improved clinical outcomes in terms of lower diabetes-related complications and were found to be associated with reduced cost (around £1715) as compared to conventional insulin aspart [50].

6.3. Insulin glulisine

Insulin glulisine (Apidra as injection vial) is a new long-acting analog having fast absorption which mimics the character of physiological insulin to a greater extent as compared to regular insulin due to the substitution of lysine amino acid at the B29 position which allows this insulin analog molecule to remain in dimeric states. Similar to regular insulin and insulin lispro, Glulisine has also shown low intra-subject variability when tested against people belonging to different ethnic groups, healthy volunteers with different body mass index and children with T1DM OR T2DM. In order to access and quantify the PK and PD aspects of Glulisine, Becker and Frick (2008) performed a study on subjects with T1DM and T2DM using euglycemic clamp method [51]. The PK data suggested insulin Glulisine possesses a Cmax of 73 μU/mL, tmax of 57 min and AUC total of 11,284 (μU·min/mL). PK data suggested that insulin glulisine showed an absorption profile having peak insulin concentration approximately twice as compared to regular insulin. Similarly, the PD data reflected insulin glulisine had glucose infusion rate (GIR)max of 6.4 mg/kg/min, GIR-AUC total of 1090 mg/kg, GIR-tmax of 114 min, demonstrating a greater rate of glucose utilization [51]. The comparative analysis of PK/PD profiles of Glulisine and aspart by two-way crossover study in T2DM patients under standard meal conditions also confirmed the association of Glulisine with lower blood glucose levels after the first meal and provided better postprandial glucose control in contrast to regular insulin when administered before and after the meal [41]. It is common to observe post aerobic workout induced hypoglycemia in diabetic patients. A randomized, single-center, open-label, crossover study of 12 patients with T2DM demonstrated the lower risk of post-exercise hypoglycemia with the treatment of insulin glulisine as compared with insulin aspart [52]. Moreover, it was also observed that insulin glulisine might be a good treatment option for children as compared to other rapid-acting insulin analogs. The study was conducted on 26 T1DM children treated with multiple daily injections or subcutaneous insulin infusion of rapid-acting insulin switched to insulin glulisine for 6 months. The mean glycated hemoglobin decreased from 7.6 ± 1.0 to 7.4 ± 0.9%, plasma glucose value improved from 183 ± 50 to 153 ± 32 mg/dL (after breakfast) and 203 ± 29 to 164 ± 23 mg/dL (after supper) and more interestingly the hypoglycemic episodes reduced from 7 ± 6 to 4 ± 4 per month [53]. Another study showed a marked improvement in glucose levels in elder (65 years or above) T2DM patients by use of insulin glulisine as prandial insulin in conjunction with insulin glargine as basal insulin. The fasting glucose levels decreased significantly (190.6 ± 73.2 mg/dL verse 138.9 ± 38.2 mg/dL) with improvement in mean HbA1c value (9 ± 1.5% verse 7.7 ± 1.1%). Therefore, it might be suggested that insulin glulisine could be of great benefit in the elderly patient as prandial insulin [54].

7. Premix insulins (including biphasic insulins)

The concept of premixed insulins was designed to reduce the total frequency of dose administration per day during treatment with rapid/intermediate-acting insulin for patient convenience. Indeed, the concept of the ideal formulation to mimic the natural release of insulin in the human comprises a mixture of rapid-acting insulin and basal insulin analog but 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 an intermediate-acting insulin [55,56]. Biphasic human insulin (BHI) contains various proportions of insulin with protamine counterpart. There is a list of most commonly available premixed insulins including biphasic human insulin (BHI; 30% regular human insulin and 70% protamine regular human insulin), biphasic insulin aspart 30 (BIAsp 30; 70 normal/30protaminated), biphasic insulin lispro (Humalog Mix 25; 75 normal/25 protamine and Humalog Mix 50; 50 normal/50 protamine). This challenge of mixing a basal and rapid-acting insulin has been conquered by Novo Nordisk in a combination of degludec/insulin aspart (70/30) under the trade name Ryzodeg [57].

8. PK and PD summary of specific analogs of premixed insulins

The comparison in PK/PD profiles of BHI with BIAsp 30 and Mix 25 revealed tmax (min)of BIAsp 30, Mix 25 and BHI has been measured as 115 ± 59, 100 ± 41 and 169 ± 71 respectively, whereas Cmax insulin (pmol/L) was observed as 415 ± 244, 360 ± 211 and 237 ± 156 for BIAsp 30, Mix 25 and BHI respectively. Additionally, the AUC (0–5 h) for BIAsp 30, Mix 25 and BHI was observed to be 1079 ± 535, 1031 ± 621 and 741 ± 426 in pmol/L.hr respectively [58]. The PK/PD profile of BIAsp30 is almost identical as BHI but has expressed a higher peak and faster absorption [59]. The active duration of a basal component for BIAsp and BHI was found to be similar, whereas the glucose-lowering potential of BIAsp was more distinct and fast as compared to BHI in healthy human [60]. A three-way study of BIAsp 30, Mix 25, and BHI revealed that PK measures and the glucose concentration of BIAsp 30treatment were closer to physiological insulin [61]. Hence, the control of HbA1c is expected to be better with BIAsp30 and same has been confirmed by Davidson et al. in their meta-analysis report of BIAsp30 versus BHI [62]. The analysis reports also suggested the overall hypoglycemia was not much differed with either of insulins (Table 1). However, the nocturnal hypoglycemia with BIAsp30 was significantly lower as compared to BMI, while the daytime hypoglycemia was significantly higher [62]. Interestingly, the comparison between BIAsp 30 and Mix 25 in patients with type 2 diabetes showed similar efficacy and safety [63].

9. Adverse effect of various insulin analogs

Indeed, the various study explored the therapeutic effect of insulin analogs with their respective onset of action and duration of effectiveness. But some studies also suggested the adverse drug reaction of some insulin analogs. Short-acting insulin analogs are reported for their adverse effect including hypoglycemia, disturbances in walking, general fatigue, rashes and bilateral leg edema (Fig. 5) [76]. Hypoglycemia is the most common adverse effect of insulin analogs observed in about 30% diabetic patients [77]. Even, frequently the hypoglycemia is endorsed by the incongruity in dose frequency and amount of administered dose of insulin, food intake, and exercise. Moreover, chronic diabetic condition, intensive insulin administration and patient history of hypoglycaemic attack also contribute to mismatch insulin dose -induced side effects [78,79]. The counter-regulation of these undesirable effects can be regulated by different combination of insulin form and dose frequency monitoring. Hypoglycemia reduces the quality of life of diabetic patients and increases the mortality and morbidity rate [80]. The rapid-acting insulin analogs including insulin aspart and insulin lispro have shown ~20% less risk of a hypoglycemic episode as compared to regular insulin [81,82]. Moreover, the double-blind investigational report of Heller et al. revealed that insulin lispro prompts significant reduction in nocturnal hypoglycemia as compared to human regular insulin [83,84].

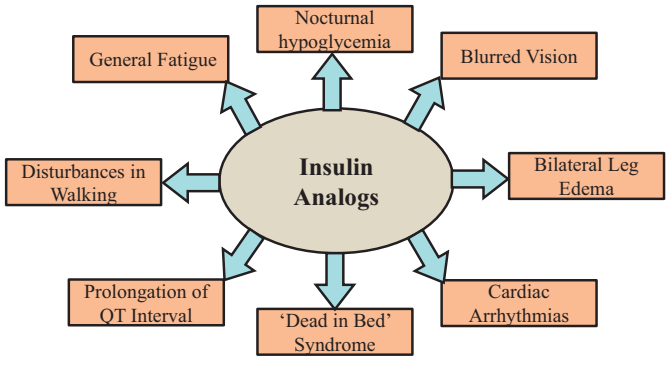

Fig. 5. Common side effects of insulin analogs due to incongruity in dose frequency and amount of administered dose of insulin.

The insensitive and incompatible insulin dose or dose frequency-induced hypoglycemia can result in a significant fall in potassium level which can lead to prolongation of QT interval and cardiac arrhythmias. The 'dead in bed' syndrome is associated with sudden substantial nocturnal hypoglycemia -induced cardiac dysrhythmias in diabetic patients [85]. Thus, the new insulin analogs having counter-regulation potential against hypoglycemia and associated dysrhythmias have been investigated for better therapeutic applications. Moreover, insulin analogs have been associated with weight gain endorsed by their anabolic effects, mild or moderate edema and rarely generalized edema and cardiopulmonary congestion [86]. Additionally, the insulin-related weight gains are also concerned with an increasing appetite and reduction of glycosuria. Furthermore, insulin injection may cause local discomfort at the site of injection including pain, skin infection and abscesses. Primarily the insulin preparations were stored in an acidic alcohol solution which may lead to impurities and other toxic contamination [87]. However, the continuous improvement in insulin purification and storage techniques significantly declined the incidence of localized side effects [88]. The immunological reactions to exogenous insulin may also cause some mild, self-limiting (resolve spontaneously) local or systemic toxicity including localized allergic reactions as itching, induration, erythema and the burning sensation at injection sites. Moreover, some systemic manifestations of allergy including urticaria and anaphylactic shock which is more severe but generally rare have been observed with insulin analogs. Immune-mediated process postulated that the local inflammatory response to insulin analogs upsurge the release of proinflammatory cytokines from the macrophages [89,90]. Although some recent reports from clinical research revealed that the use of insulin analogs have been found to be safe, effective and associated with significant improvement in patient satisfaction [91,92]. But continuous improvement is still needed to avoid the reported adverse reaction of insulin analogs. The advanced insulin analogs (premixed insulin analogs) significantly reduce the chances of hypoglycemia, especially to nocturnal episodes, weight gain and other adverse effects [93,94].

10. Conclusion

The long-acting insulin analogs provide longer duration of action ~24 h and reproducible serum concentration when compared with NPH insulin, these properties mimic the basal slow and steady release of insulin for narrow glucose level corrections. Rapid-acting insulin analogs get absorbed rapidly, attained peak quickly and have the shorter duration of action as compared with regular human insulin. These properties mimic the insulin surge in prandial phase in response to glucose excursions. Premixed insulin analogs provide with a more and faster glucose lowering capabilities as compared to premixed human insulin. Long-acting analogs have a relatively lower risk of hypoglycemic episodes as compared to NPH insulin and rapid-acting. Premixed analogs improved glycemic control on convenient dosing as compared to normal human insulin particularly for post-prandial glycemic control. Therefore, treatment with analogs provides an improved and balanced glycemic control, lower risk of hypoglycemia, great flexibility in term of dosing, resulting in increased patient convenience. However, there is still a gap for improvement in term of dosing frequency, nocturnal glycemic control and rapid prandial action to come closer to the natural human insulin physiology.

As incidences of diabetes tend to increase with towering prevalence, more effective insulin therapies are of great need. The major concerns with these insulin therapies are adequate glycemic control with simple and convenient dose regimen and no episodes of hypoglycemia to reduce omission or delays in therapy. Basal insulin analogs are much similar to this ideal approach of treatment as insulin degludec offer single administration per day with the reduction in episodes of nocturnal hypoglycemia. Additionally, Insulin glargine and Insulin detemir also

provide adequate glycemic control, lesser hypoglycemic episodes risk in comparison to NPH. The development of rapid-acting insulin analogs allowed faster absorption of insulin into circulation from the subcutaneous injection site. Moreover, the development path of basal insulin peglispro (BIL) provides a great basis to improved glucose normalization, prandial insulin dose reduction and reduced hypoglycemic episodes but the development of BIL was ended due to suspected liver steatosis and nonalcoholic steatohepatitis (NASH) like status. Intriguingly, the oral insulin in the pipeline had shown remarkable development. Approval of oral insulin will enhance dose compliance and glycemic control. However, a great invention comes with the price, which questions the availability of this formulation to the major group of the patient suffering from diabetes. Nevertheless, Insulin formulations will always have some scope of improvement due to the complexity of natural insulin physiology regulation, insulin regimens, the complexity of disease, diversity of patient, diets controls and last but not the least cost-effectiveness of a formulation. At the end of the day, knowledge and ability of a practitioner to manage patients` insulin regimen is of prime importance in treating diabetes.

CRediT authorship contribution statement

Arun K. Sharma: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Validation, Writing - original draft, Writing - review & editing. **Gaurav Taneja:** Formal analysis. **Gunjan Sharma:** Data curation, Investigation, Methodology. **Aakash Deep:** Writing - review & editing.

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Conflict of interest

Authors declared no conflict of interest.

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