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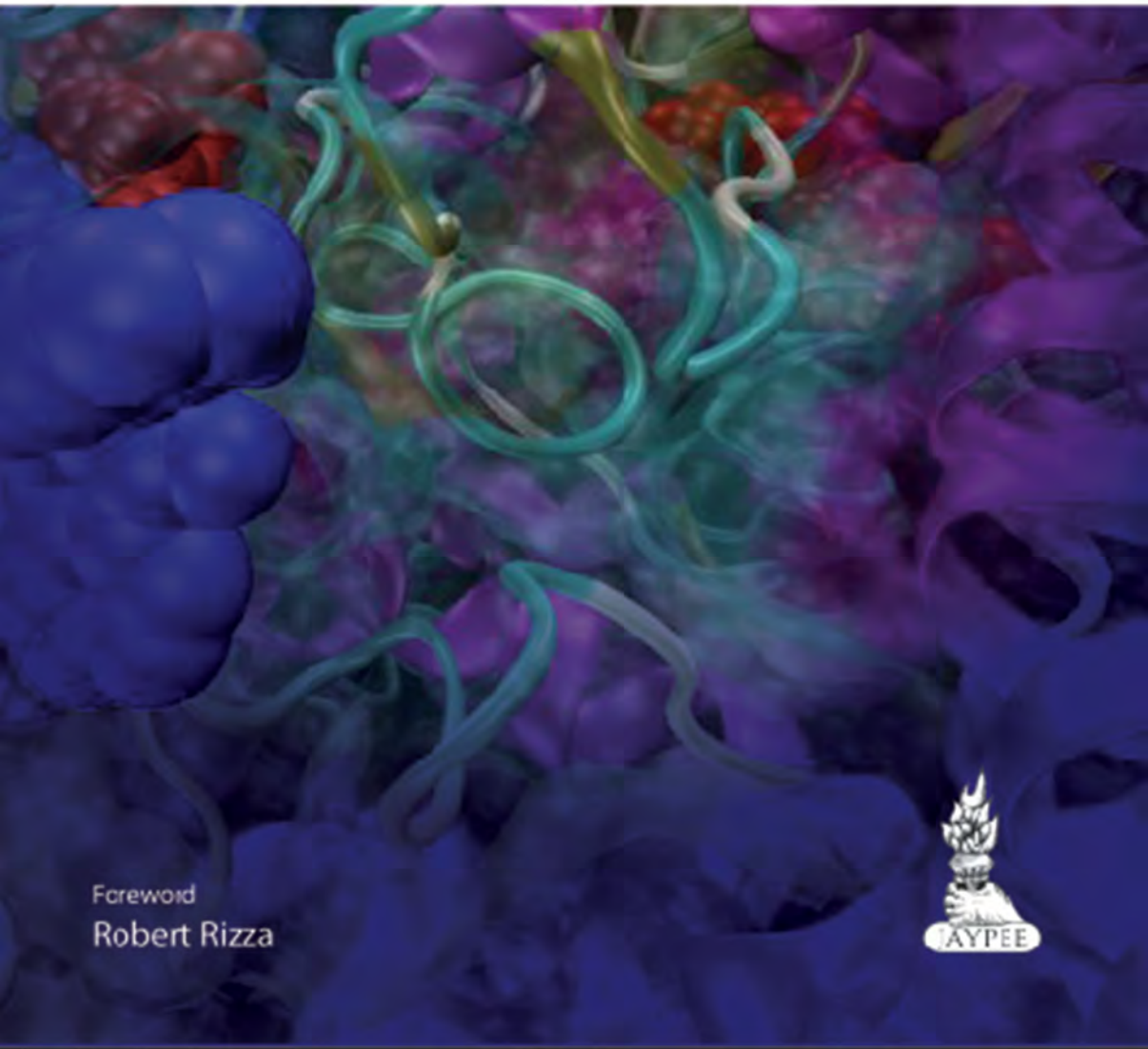
INSULIN THERAPY
CURRENT CONCEPTS



Foreword
Robert Rizza

JAYPEE

Contents

Contributors *ix*
Foreword *xi*
Preface *xiii*

1. **The History of Insulin Therapy** **1**
Shama Mahendru, Ambrish Mithal

2. **Physiology of Insulin Secretion and Action** **8**
Monashis Sahu

3. **Insulin Types and Pharmacokinetics** **16**
Ganesh Jevalikar, Suchitra Behl

4. **Insulin Analogs** **26**
Jasjeet S Wasir

5. **Advances in Insulin Delivery Devices** **39**
Ramchandra Naik, Arundhati Dasgupta

6. **Insulin Therapy in Type 1 Diabetes** **52**
Ganesh Jevalikar

7. **Initiation and Intensification of Insulin Therapy in Type 2 Diabetes** **68**
Sunil K Mishra, Ambrish Mithal

8. **Insulin Therapy for Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State** **82**
Gagan Priya

9. **Insulin Therapy in Hospitalized Patients** **103**
Beena Bansal, Ambrish Mithal

10. **Insulin Therapy in Special Situations** **112**
Pankaj Shah, Julie Probach, Tricia Veglahn

11. **Adverse Effects of Insulin Treatment** **129**
Vaishali S Naik, Ambrish Mithal, Ganesh Jevalikar

***Appendix 1*: Storage of Insulin** **143**
Shubhda Bhanot

***Appendix 2*: Insulin Injection Sites** **145**
Shubhda Bhanot, Ganesh Jevalikar

***Appendix 3*: Injection Technique, Needle Reuse, and Needle Disposal** **147**
Shubhda Bhanot

***Appendix 4*: Guidelines on Safe Use of Insulin in Hospital** **155**
Beena Bansal

***Appendix 5*: Peri-operative and Peri-procedure Orders for Type 2 Diabetes Patients Undergoing Surgery Under GA (e.g., Coronary Artery Bypass Grafting)** **157**
Beena Bansal

***Appendix 6*: Peri-operative and Peri-procedure Orders for Type 2 Diabetes for Procedures Under Regional Anesthesia When NPO for Less than Half Day** **159**
Beena Bansal, Ganesh Jevalikar

***Appendix 7*: Glucose Monitoring Chart for Patients on Subcutaneous Insulin** **160**
Beena Bansal

Index *163*

4

Insulin Analogs

Jasjeet S Wasir

ABSTRACT

Insulin analogs are synthesized by changes in the structure of insulin molecule and are not similar to any naturally occurring insulin.

Rapid-acting insulin analogs (lispro, aspart, and glulisine) have rapid onset of action (5–15 min), higher and earlier peak concentration levels leading to more physiologic insulin action compared to regular insulin. Long-acting analogs glargine and detemir have relatively peakless action profile compared to neutral protamine Hagedorn and lesser day to day variability which makes them more suitable as basal insulins. Premixed formulations of insulin offer advantages of convenience of administration particularly in elderly and visually impaired subjects but are not ideally suitable for type 1 diabetes.

Degludec is the recently launched novel basal insulin with ultra-long duration of action and even lesser variability which is expected to further reduce occurrence of hypoglycemia.

INTRODUCTION

Insulin was first used for treatment of diabetes in 1922 in Canada. However, our ability to mimic physiological insulin secretion remains a challenge. Landmark studies like diabetes control and complications trial (DCCT) have clearly demonstrated superiority of physiologic insulin replacements over conventional twice daily treatment. Attempts to make insulin therapy more physiological include change in the sources (animal to human), delivery devices (insulin pump), and structure (newer insulin analogs).

Physiological insulin secretion (Fig. 1) consists of basal component which limits hepatic glucose production and prandial component which is secreted in response to meals. Ideal basal insulin, therefore, should not have a peak level and ideal prandial insulin should have similar concentration, peak action, and duration of action as endogenous insulin. In this regard, limitations of conventional insulin include:

- A lag phase from administration to onset of action

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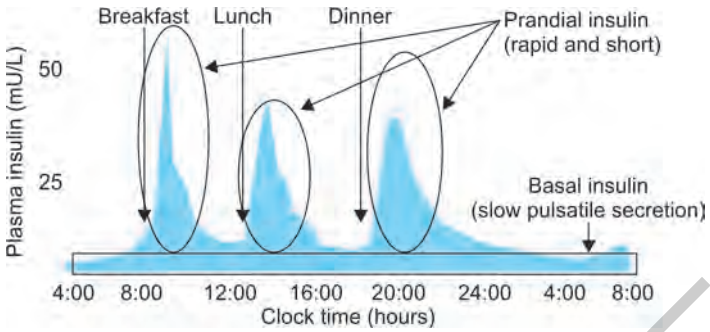

Fig. 1: Physiological secretion of endogenous insulin.

- Unphysiologic action profiles causing fluctuations in blood glucose (BG)
- Variability in the action between subjects and within subject.

To overcome some of these problems, research has led to production of newer insulin analogs. These are synthesized by changes in the structure of insulin molecule and are not similar to any naturally occurring insulin. In this chapter, structure, pharmacokinetics, pharmacodynamics, clinical uses, and possible concerns of currently available insulin analogs are discussed.

STRUCTURE

While designing insulin analogs, recombinant bioengineering methods are used to make structural changes into the parent insulin molecule (amino acid substitutions, inversions, or additions of amino acids or side chains) which modify the amino acid sequence. This changes pharmacokinetic properties of the resultant molecule leading to change in selfssss-aggregation and rate of absorption from subcutaneous (SC) space. The changes, however, do not affect receptor binding, postreceptor signaling, and antigenic properties of insulin. Based on the rate of diffusion from SC tissue, insulin analogs can be classified as rapid-acting and long-acting. The analogs in current clinical use with their structure and pharmacokinetic properties are listed in table 1. Premixed formulations of rapid-acting analogs with protaminated analogs in various proportions line 30/70, 25/75, and 50/50 are also used commonly in type 2 diabetes. The names of analogs give some hint at the structural changes; e.g., "lis-pro" indicates change in lysine and proline, "aspart" indicates addition of aspartic acid, "glu-lisine" indicates changes involving glutamic acid and lysine, and "gl-argine" indicates changes involving glycine and arginine.

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Table 1 Insulin analogs in current use

*Insulin preparation**	*Structural change*	*Onset of action*	*Peak action*	*Duration of action*
Rapid-acting				
Lispro	Transposition of lysine at B29 with proline at B28	5–15 mins	30–90 mins	3–5 hrs
Aspart	Replacement of proline at B28 with aspartic acid	5–15 mins	30–90 mins	3–5 hrs
Glulisine	Replacement of lysine at B29 by glutamic acid and asparagine at B3 by lysine	5–15 mins	30–90 mins	3–5 hrs
Long-acting				
Glargine	Replacement of asparagine at A21 with glycine and addition of two arginine residues at B30	1–3 hrs	Peakless¶	24 hrs†
Detemir	Deletion of threonine at B30 and acylation and addition of myristic acid to lysine at B29	1–3 hrs	Peakless¶	24 hrs†

*Names in parentheses indicate common brand names available in India.
¶A small peak (much less than neutral protamine Hagedorn) can be seen with both glargine and detemir.
†Duration may not be 24 hours in all patients.

RAPID-ACTING INSULIN ANALOGS

The amino acid modifications in the currently available rapid-acting analogs are done in B chain of insulin molecule and include transposition of lysine on B chain at position 29 (B29) with proline at position 28 (Lispro), replacement of proline at position B28 by the negatively charged aspartic acid (Aspart), or replacement of lysine at B29 with glutamine and asparagine at B3 with lysine (Glulisine).

Pharmacokinetic Properties

Human regular insulin tends to form hexamers in solutions. Various factors like structure of molecule, presence of zinc, insulin concentration, and pH of solution affect hexamer formation. Before absorption, hexamers dissociate into dimers and monomers which diffuse across capillaries rapidly and are biologically active (Fig. 2). Modifications in rapid-acting analogs decrease the propensity to self-aggregate through charge repulsion, hence the analogs exist predominantly in a monomeric form (Fig. 2) leading to faster absorption, early and higher peak, short duration of action, and lesser variability in

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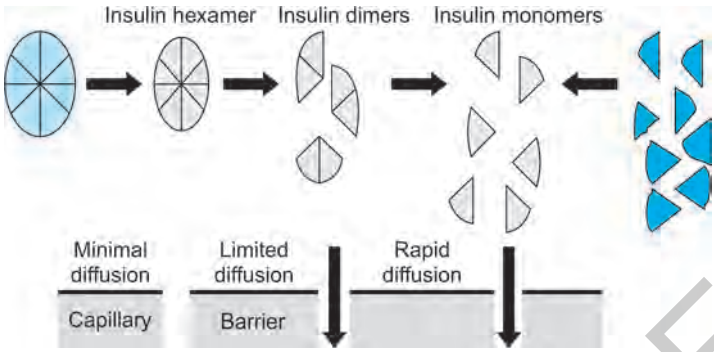

Fig. 2: Subcutaneous absorption of regular (grey) and rapid-acting (dark blue) insulin.

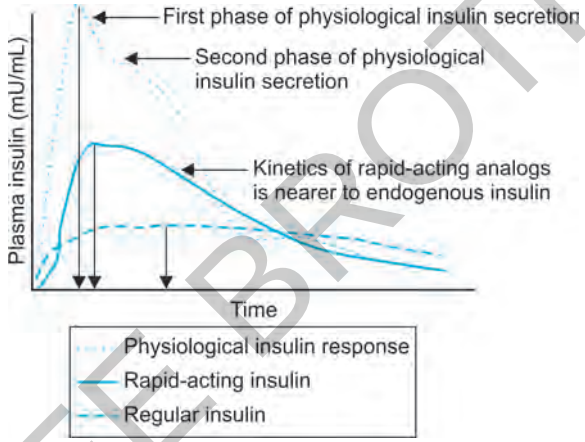

Fig. 3: Comparison of endogenous insulin, analogs, and standard insulin.

concentration achieved thus mimicking endogenous insulin more closely than regular insulin (Fig. 3).

Factors which modifying absorption of human insulin after a SC injection like age, thickness of SC fat, injection site, local circulation, exercise also influence absorption of analogs in a similar way. Like regular insulin, insulin analogs are metabolized in liver and kidney and excreted in urine. Hence, renal dysfunction delays excretion and prolongs insulin effect.

Pharmacodynamic studies using glucose infusion rates (GIR) in euglycemic clamp studies have demonstrated time to reach peak concentration (t_{max}) almost half that of regular insulin, peak concentration double that of regular insulin, and shorter residence time. This translates into better control of postprandial glucose and shorter time of action, hence lesser risk of delayed hypoglycemia. After SC injection, the action of rapid-acting analogs

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starts at 5–15 min, peaks at 60–90 min, and is over by 4 hours (Table 1). All three analogs (1) lispro, (2) aspart, and (3) glulisine have more or less similar pharmacokinetics and action.

Clinical Use of Rapid-acting Insulin in Diabetes Mellitus

Type 1 Diabetes Mellitus (Also See Chapter 6)

Type 1 diabetics have no insulin reserve beyond the honeymoon phase. Hence, insulin replacement should be matched to physiological insulin secretion as far as possible. Best way of doing this is continuous subcutaneous insulin infusion (CSII) or multiple subcutaneous insulin injections (MSI). Superiority of these regimens has been proven by the DCCT study. These regimen consist of prandial boluses given before each of the major meals or snacks, basal insulin that regulates lipolysis and hepatic glucose output, and correction-dose insulin (usually small dose as compared to prandial or basal) to address in between-meal hyperglycemia, independent of the prandial insulin.

Endogenous insulin response to meals occurs in a robust first-phase secretion and then a more prolonged second-phase release. Subcutaneous injection of rapid-acting insulin analogs mimics the first phase of insulin secretion; however, it will never precisely replicate the second-phase release. Based on the kinetics and duration of action of the currently available insulin preparations, regular and neutral protamine Hagedorn (NPH) insulin span both the prandial and basal components of insulin replacement, whereas insulin analogs (rapid- and long-acting) target each of these components separately.

In keeping with pharmacokinetic properties, potential indications of rapid-acting analogs in type 1 diabetes are summarized in table 2.

Table 2 Potential indications of rapid-acting analogs in type 1 diabetes

• Insulin pump therapy
• Prandial or correction doses in MSI regimen
• Infants, toddlers and young children (unpredictable eating habits)
• Sick day management and correction boluses
• Known or suspected delayed or nocturnal hypoglycemia
• Unwillingness or inconvenience of waiting for injecting 20–30 mins before meals
• Avoidance of extra mid-meal or bedtime snacking
• Postprandial hyperglycemia despite of regular insulin dose and timing adjustment

MSI, multiple subcutaneous insulin injections.

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Although regular insulin can be used in pumps and for correction doses, rapid-acting analogs are more suitable for this. When used in insulin pumps (CSII), the rapid-acting insulin preparations when given continuously mimic the basal insulin profile. Use in young children with unpredictable eating habits makes it possible to administer insulin after meals, hence reducing risk of hypoglycemia or hyperglycemia. Several studies in type 1 diabetes have shown that rapid-acting analogs are associated with improved flexibility, reduction of severe hypoglycemic episodes, and decreased postprandial hyperglycemic events resulting in improved quality of life.

Most of the studies and meta-analysis comparing rapid-acting analogs with regular insulin have shown no or minimal benefit in terms of glycemic control as measured by glycosylated hemoglobin (HbA1c) (-0.1 to -0.2% in favor of analogs). Benefits are more with pump therapy than with MSI. Similarly, incidence of mild hypoglycemia has not been proven to be significantly less with their use. In addition to this, with long meal gaps, the premeal readings may become high due to short duration of action. Basal insulin doses may not adequately control blood glucose in this time period particularly if snacks are unaccompanied by a bolus dose. Similar problem may occur with fatty meals and diabetic gastroparesis where regular insulin's tailing effect might be of benefit. Cost of these insulins is nearly 3–4 times higher than conventional insulins and is a major impediment to its widespread use particularly in developing countries.

Rapid-acting Analogs in Type 2 Diabetes

Rapid-acting insulin analogs have a limited role in the conventional treatment of type 2 diabetes. Indications for their use are essentially similar to indications of human regular insulin (with advantages as noted above) and include the following:

- Patients with acute illness or complications (e.g., severe acute coronary syndromes, pyelonephritis, lower respiratory tract infections, hyperglycemic hyperosmolar state, etc.) of diabetes
- Patients with advanced end-organ damage, e.g., chronic kidney or liver disease, and congestive heart failure
- Secondary failure of oral agents in those who are also receiving basal insulin
- At diagnosis in patients with severe osmotic symptoms and uncontrolled hyperglycemia [the new diabetes management guidelines (American Diabetes Association, International Diabetes Federation, and American Association of Clinical Endocrinologists) endorse early use of insulin for fast and effective glycemic control for prevention of complications].

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When used in type 2 diabetes, rapid-acting analogs potentially can give better postprandial control, improved flexibility, and some reduction of severe hypoglycemic events. However, clear superiority of insulin analogs in glycemic control and diabetes complication rate is not proven.

LONG-ACTING INSULIN ANALOGS

Structure and Pharmacokinetics

Based on the basal physiological insulin, the optimal characteristics of "ideal" basal insulin should include the following:

- The pharmacodynamic profile should be flat (peakless) and should be associated with a low risk of hypoglycemia (e.g., commonly seen with NPH insulin the phenomenon of nocturnal hypoglycemia due to peak activity occurring several hours after injection)
- The duration of action should be around 24 hours to control fasting plasma glucose with just one daily injection
- Variability within individual patients should be low, meaning that identical doses of insulin administered to the same patient on different occasions should lead to identical and predictable effects, thus lowering the risk of hypoglycemia or hyperglycemia.

Insulin Glargine

Based on the above mentioned principles, long-acting insulin analogs were developed towards the end of the 20th century (glargine was the first to be introduced in 2001).

Insulin glargine differs from human insulin at position A21 of the A chain (substitution of asparagine with glycine) and position B31 and B32 of the B chain (addition of two arginines). These changes shift the isoelectric point (pH at which insulin exists in a soluble state) from pH 5.4 to pH 6.7. Insulin glargine is injected as a clear acidic solution (pH 4), which forms microprecipitates that must dissolve before absorption can take place. Precipitation and slow redissolution are inherently associated with substantial variability. Nonetheless, the time-action profile of insulin glargine is flatter and of longer duration compared with NPH insulin (Fig. 4).

Insulin Detemir

The other long-acting insulin analog available is insulin detemir. Manufacture of detemir involves removal of threonine at position B30 and acylation of lysine at B29 with a 14-carbon fatty acid (myristic acid). The prolonged duration of action for insulin detemir is attributable to a combination of increased self-association (hexamer stabilization and

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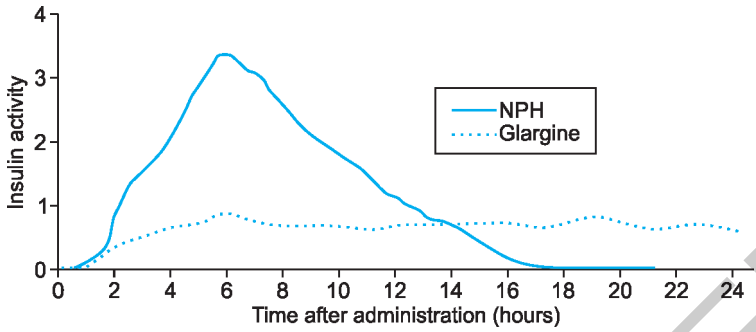

Fig. 4: Pharmacokinetic profile of glargine versus neutral protamine Hagedorn (NPH) insulin.

hexamer-hexamer interaction) and albumin [detemir is highly albumin-bound (98.8%), binding because of the acylation]. The analog is supplied as a clear neutral solution and remains in solution in the subcutaneous depot, in the circulation and in the target tissues until interaction with the insulin receptor. Absorption of insulin detemir is, therefore, dependent on neither appropriate resuspension before injection and dissolution of crystals, as is the case with NPH insulin, nor on formation and redissolution of microprecipitates, as is the case for insulin glargine. As compared to NPH insulin, detemir is longer-acting and has a flatter action profile. However, the duration of action is shorter than glargine needing twice daily dosing in many patients. Advantages compared to glargine include lesser within subject variability and lesser weight gain.

Clinical Uses of Long-acting Analogs

Type 1 Diabetes Mellitus

Long-acting insulin analogs are used as basal insulin in MSI regimen in type 1 diabetics along with prandial boluses of regular insulin or rapid-acting analogs. Basal insulin requirement is generally 40–50% of total daily dose and is given as a single daily dose. Twice daily dosing may be required especially with detemir. The dose can be administered at any time of the day (morning, evening, or bedtime) but it is important that it is given at same time each day.

Advantages of long-acting analogs include convenient dosing, no need of mandatory snacking (as with peak level of NPH), improved flexibility, and reduced risk of severe and nocturnal hypoglycemia. The reduced rates of hypoglycemia seen with long-acting analogs make the dose increments easier so as to achieve greater degree of glycemic control at a lesser risk (hypoglycemia).

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Several clinical studies comparing long-acting analogs with NPH have shown small but significant improvements in HbA1c. For example, in an observational study of 1,942 patients who were switched from NPH insulin to insulin glargine, mean HbA1c declined by 0.8% over 6 weeks of treatment from 8.0% at baseline. In a second study of longer duration, 1,447 patients who were switched from various insulin regimens to basal-bolus therapy with insulin glargine and insulin glulisine experienced a significant mean reduction in HbA1c of 1% over 6 months from a baseline of 8.0%. However, this improvement is not consistent across all the studies. A recent meta-analysis did not find significant differences between long-acting analogs and NPH in children and adolescents with type 1 diabetes.

Disadvantages of long-acting analogs include higher cost (6–7 times more costly than NPH). Mixing of these insulins with short-and rapid-acting insulin is not possible with present formulations as it leads to significant blunting of effects of the latter. Being an acidic solution, glargine is sometimes associated with a stinging or burning sensation at the injection site.

Type 2 Diabetes Mellitus

Landmark studies like the United Kingdom Prospective Diabetes Study have clearly shown that early and intensive glycemic control is associated with better outcomes. This clearly defines the role of early and aggressive glucose lowering therapy including insulin in type 2 diabetes. Interestingly, in reality only a small percentage of type 2 diabetics are on basal insulin. This may reflect the general trend of using insulin as a last resort in controlling hyperglycemia and reluctance on part of both the patient and the physician until two or even three oral agents have failed to achieve glycemic control. However, progressive nature of β-cell loss in type 2 diabetes is well known and early use of insulin may help in preservation of β cells, reduce apoptosis, decrease glucotoxicity, reduce cytokines, atherosclerosis, and have beneficial effect on the lipids and blood pressure.

Long-acting analogs are used as basal insulin, in combination with oral antidiabetic drugs and as basal-bolus therapy with prandial insulins in advanced insulinopenic type 2 diabetes, during periods of surgery or stress and ketoacidosis.

Advantages of long-acting insulin analogs in comparison to NPH in type 2 diabetes:

- More physiological profile of long-acting insulin analogs as compared to human insulin (NPH)
- Less hypoglycemia as compared to human insulin
- Greater flexibility in timing of injections.

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Based on these advantages, long-acting analogs have found its place right at the top of the treatment algorithm for diabetes. All the major associations including American Diabetic Association, American Association of Clinical Endocrinologists, International Diabetes Federation and European Association for the Study of Diabetes have endorsed this superiority in their treatment guidelines. In summary, the guidelines clearly state that in addition to metformin and therapeutic lifestyle changes long-acting insulin may be added in preference to other oral agents if HbA1c is in between 8 and 10%, patient has severe osmotic symptoms (e.g., weight loss), if fasting glucose is >250 mg/dL or the random BG levels are consistently >300 mg/dL. Finally, prandial insulin may be added along with basal insulin in patients with HbA1c >10%.

PREMIXED ANALOGS

These are fixed mixtures of rapid-acting analogs with their protaminated component in various proportions. Three formulations commonly available include: (1) 50% lispro/aspart +50% protaminated lispro/aspart (Humalog® Mix 50/50, Novomix 50) (2) 25% lispro +75% protaminated lispro (Humalog® 25/75), and (3) 30% aspart +70% protaminated aspart (Novomix 30/70). Due to distinct pharmacokinetics of rapid-acting analogs, in comparison to conventional premixes of human insulin, premixed analogs have more desirable pharmacokinetic and pharmacodynamic profile, leading to better postprandial glycemic control. Flexible injection timing in relation to meals is likely to improve adherence to therapy. HbA1c levels and rates of hypoglycemia are comparable to conventional premixes. Both premixed analogs and conventional premixes are suitable for type 2 diabetics who are elderly, have poor vision, and poor hand eye coordination or are noncompliant to physiologic insulin regimen. They are not ideal for type 1 diabetes as separate adjustment of two components is not possible and a comparatively rigid lifestyle is necessary.

INSULIN ANALOGS AND CANCER

Type 2 diabetes appears to be associated with increased risk of cancers like breast, colorectal, and pancreatic cancer. Insulin has been shown to have growth promoting effect on cancer cells in laboratory studies. Concerns of association between insulin analogs and cancer stem from epidemiologic studies reporting increased risk of some cancers in patients treated with insulin glargine. Methodological limitations and confounding factors like diabetes, obesity, and sedentary lifestyle make interpretation of these

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findings difficult. Plausible mechanisms for cancer risk with analogs are due to increased affinity to insulin-like growth factor-1 (IGF-1) and altered binding kinetics leading to growth promoting effect. In general, evidence linking or excluding relation between analogs and cancer is limited. Most of the professional societies recommend that cancer risk should not be a deterrent to choosing appropriate antidiabetic treatment including insulin.

RECENT ADVANCES

Degludec

Currently, used long-acting analogs have advantages over NPH in terms of relatively peakless profile and lesser variability. But it is well understood now that the action may not be entirely peakless, particularly at high doses. In addition, the duration of action may fall short of 24 hours needing twice daily dosing, particularly with use of detemir in type 1 diabetes. Hypoglycemia continues to be the most significant barrier to good glycemic control in both type 1 and type 2 diabetes. Degludec an ultra-long acting insulin has recently been developed which may in the near future effectively take care of some of the existing limitations of the approved long acting insulins. At the time of writing this chapter, degludec has been approved for use in European Union for use more than 18 years of age in both type 1 and type 2 diabetes as well as in India.

Structure and Pharmacokinetics

Insulin degludec differs from human insulin in deletion and threonine at B30 position and addition of hexadecandioyl (fatty diacid) moiety attached to lysine at B29 via a glutamic acid spacer. After injection in subcutaneous space, after dispersion of phenol, it forms large soluble multihexamers from which insulin monomers dissociate at a slow and steady rate. This leads to a longer half-life (approximately 25 hours) and a glucose lowering effect of more than 40 hours at steady state.

In comparison to insulin glargine, degludec has longer duration of action and importantly, lesser pharmacodynamic variability. Regimens like thrice a week regimen or variable timing regimen have been studied but not recommended at present in clinical practice.

Degludec in Type 1 Diabetes

In an open label, treat to target, noninferiority trial, reduction in HbA1c with degludec was, not inferior to glargine. Rates of nocturnal hypoglycaemia were 25% lower in degludec group compared to glargine but overall hypoglycaemic

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events were not different. A recent study has reported once daily flexible dosing to be as effective as glargine but at present in clinical practice, once daily regimen is advised preferably same time everyday.

Degludec in Type 2 Diabetes

Evidence from two randomized controlled trial has shown degludec to be noninferior to glargine in terms of HbA1c reduction. Rates of nocturnal and severe hypoglycemia were shown to be significantly lesser with degludec. In comparison to sitagliptin, degludec had better glycemic control but increased occurrence of hypoglycemia.

Insulin degludec is given once daily at any time of the day, preferably at the same time every day. On occasions when this is not possible, there can be some flexibility in the timing of insulin administration. The summary of product characteristics states that a minimum of 8 hours between injections should always be ensured.

Insulin Degludec/Insulin Aspart (IDegAsp)

One of the unique advantage of degludec over other basal analogs is its miscibility with short-acting analogs. IDegAsp is a mixture of degludec and aspart in 70/30 percentage and has been shown to be equally efficacious to glargine in type 2 diabetes.

In keeping with available evidence, degludec use can be considered in adults (age>18 years) with type 1 or type 2 diabetes, particularly in presence of repeated nocturnal hypoglycaemias despite titration of insulin.

Some other analogs under development are discussed in chapter 3.

CONCLUSION

Development of long- and short-acting analogs of insulin is an important milestone in the history of insulin. This is a step closer to making insulin therapy more physiological. Insulin analogs have more physiological pharmacokinetic and pharmacodynamic profile. They provide increased flexibility in terms of injection timing and less rigid requirement of snacking. Risk of severe and nocturnal hypoglycemia is lesser compared to conventional insulins. Till date, benefit in terms of glycemic control as measured by HbA1c is at best modest. The possible link between insulin analogs and cancer has limited evidence and needs more epidemiologic and observational studies. This should not be a deterrent in choosing best therapy for a patient. Ongoing developments and newer analogs are being developed and the quest for making insulin therapy physiological continues.

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INSULIN THERAPY
CURRENT CONCEPTS

Key Features

- A crisp and exhaustive review of various aspects of insulin use in the diabetic population
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- Well conceived to meet the clinician's needs in optimizing the use of insulin in managing diabetes
- An elaborate discussion on insulin analogs, their place in therapy, and the future of these molecules
- Summarizes the available evidence on insulin use in modern day practice
- Insights in to the place and optimal use of insulin delivery devices in modern day management of diabetes
- Targets diabetologists as well as physicians interested in the practice of diabetology.

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