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Role of New Insulin Analogs in the Management of Diabetes. A Clinical Review

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Review Article

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Abstract

This paper has reviewed different insulin analogs currently available in the market and pharma industry, their safety, efficacy and their roles in the diabetes management, comparing with human regular and NPH insulin. Traditional insulins (human regular and NPH insulins) do not have constant or smoother pharmacokinetic and pharmacodynamic profiles and are usually associated with erratic blood glucose profiles with hypoglycemia or hyperglycemia when compared with analog insulins. Similarly they do not match physiologic insulin profiles with basal bolus format. According to the medical literature, current insulin analogs are more efficacious and also it has been documented in research trials that recent insulin analogs are better and safer as compared to human regular and NPH insulin in terms of hypoglycemia and HbA1c reductions. Hence this paper has reviewed these insulins analogs (longer acting basal and rapid acting insulin analogs) for their safety and efficacy in terms of hypoglycemia and HbA1c control, for the management of both type-1 and type-2 diabetics in hospitals and clinics.

Keywords: Diabetes; Human Insulin; Analog Insulin's; Hypoglycemia; HbA1c

Abbreviations: RAI: Rapid Acting Insulin Analogs; CSII: Continuous Subcutaneous Insulin Infusion.

Introduction

Diabetes Disease, Traditional and Analog Insulins

Diabetes Mellitus is a clinical syndrome characterized by hyperglycemia due to insulin deficiency and insulin resistance [1-4]. Good metabolic control is essential to prevent complication of diabetes [5]. Type-1 diabetics require only insulin to control glucose metabolism mostly basal bolus regimen. However, type-2 diabetics, due to insulin resistance, also require oral agents (such as metformin) to control blood glucose [6,7]. Clinical experience has shown that most of these type-2 diabetic patients will require also insulin over the time in combination with oral agents if good glycemic control is not achieved. They may require only basal insulin initially, then mixtures of insulins, two times daily,

and finally some will be managed by basal bolus regimens as well [8].

Regarding analog insulins, they are very similar to human insulin, however, their one or two amino acids are changed by biotechnology and genetic engineering methods. In recent years, several insulin analogs injections have been developed. However, in clinical practice most of the physicians still use human regular insulin and NPH insulin or combination of them (Humulin 30/70). Our aim in this review is to highlight the role of current available insulin analogs (rapid acting and longer acting insulin analogs) in the management of diabetes, their efficacy and safety in terms of hypoglycemia and HbA1c reductions. Current topic has not been reviewed in the past in such a manner and this review will significantly contribute to the scientific literature and to the diabetes physicians so that they can clinically judge which insulin is more efficacious and safe in their clinical practice while managing diabetes in hospitals and clinics.

Methods and Literature Review

This is a scientific review article, comparing different insulins currently available in the pharmaceutical industry. Time duration of literature search was four months, from January 2022 until April 2022. For literature review of various insulins, different studies and research trials were searched on the internet from PubMed from the year 1920 until 2022. The search criteria for articles were the terminologies, including "insulins", "hypoglycemia" "HbA1c", "insulin analogs". Only free full text papers in English language were selected. Out of 257 results, 74 studies were short listed and selected focusing on newer insulin analogs and their comparison with other insulins. After detailed study from the research papers text, main conclusions were drawn comparing human insulins (regular and NPH) with that of current long acting and rapid acting insulin analogs (RAIs). Also different variables such as Insulin types, HbA1c, Hypoglycemia, Plasma glucose were also studied in this review with their scientific applications and these variables were also discussed among different insulins, for their safety, efficacy and flexibility of use in the selected literature.

Clinical Management of Hyperglycemia by Insulins

Diabetes mellitus is a hyperglycemia syndrome with different etiologic presentations, a condition which must be diagnosed specifically before targeted treatment (insulin/oral agents) is initiated and prescribed to the patient. According to the literature review, we have found that recent insulin analogs are safer and efficacious than human insulins in terms of hypoglycemia and HbA1c reductions and for better diabetes control. Initially for the commercial use, insulin was extracted from porcine and bovine pancreata, with a purity of 80 - 90%, with some major contaminants and allergens. Hence, such insulin was associated with immune- mediated reactions, especially lipoatrophy, antibody mediated insulin resistance with swelling and pain at the site of injection, ultimately affecting the kinetics of insulin absorption and action [9]. In the medical research and literature history, industrial synthesis of human insulin was done by three techniques. The earliest one involved isolation of insulin directly from human cadaveric pancreata and thereafter purifying it i.e., methods for separating insulin from non-insulin protein [10]. But due to unavailability of human tissue, this technique did not provide sufficient quantities for commercial insulin preparation. The other technique so called "semi- synthesis", chemically converts porcine/bovine insulin to the human insulin sequence via substitution of the one amino acid in the primary sequence [11]. Lastly, in 1980, recombinant DNA technology was patented and introduced and human insulin became widely available commercially. This technique involves insertion of human DNA sequence into bakers' yeast or bacteria Escherichia coli and thereafter genetically programmed to synthesize the insulin molecule [12-14]. Hence, this insulin is called human insulin. The insulin produced by this technique is then purified to ~ 99.9% via chromatography columns, ultimately eliminating immune - mediated side effects. Advancement from animal to human insulin has reported greater degree of hypoglycemia in some patients [15,16]. But up to date systemic reviews and research studies have not proven this fact [17,18].

Regarding Industrial Evolution of Insulin and soluble and long - Acting Insulin Preparations, in the past, duration of action of soluble insulin was prolonged by adding modifying agents [19]. But at the same time this was associated with pain and swelling at the site of injection. Therefore, clinically only one injection was given to the patient to meet daily insulin requirement. However, this methodology was clinically difficult because kinetics of absorption and insulin action were variable and unpredictable. Then later on, a new method was introduced of making insulin a poorly soluble complex thus reducing its absorption from site of injection [20-22]. Furthermore, small amount of zinc was added to stabilize this complex thus maintaining the duration of action for 24 hours. This resulted in constant rate of absorption and duration of action lasting for 12-24 hours, and was named isophane or neutral protamine Hagedorn (NPH) [115,116]. In later years, semilente, and lente insulins were produced by the same methodologies [23-25]. This was one of the famous and widely used insulin preparations available at that time.

Regarding Human Soluble insulins and Rapid Acting insulin Analogs (RAI), also there was extensive research was conducted to make insulins more compatible for human use. Following injection, insulin containing fluid moves

via osmosis, leading to dilution with dissociation of the insulin molecules. This gradual process facilitates insulin molecules to be transported across the capillary walls into circulation as monomers [26,27]. Because of this slow process of diffusion, patients are advised to inject soluble insulin at least 30 minutes before a meal so that enough insulin is available to circulation when blood glucose levels rise, immediately after when meals is absorbed. For many patients this technique is difficult to follow i.e., to inject insulin prior meal approximately half an hour, especially in case of children with greater risk of hypoglycemia. Hence, great care and meal planning is required especially in type-1 diabetic children.

To overcome this difficulty, extensive research at molecular level was conducted during the last two to three decades. We have extensively reviewed pharmacokinetics and pharmacodynamics of different insulins. The biologic action of insulin can be reduced by producing specific changes in amino acid sequence of insulin molecule via genetic engineering recombinant DNA technology [28]; thus dissociation rate constants from receptors are increased relative to human insulin. These analogs dissociate faster and absorb rapidly from site of injection to the blood circulation and patient can inject insulin just 5-10 minutes prior to meal [29]. This technique is even more flexible for the patients and especially in case of type-1 diabetic children. This insulin is called Rapid Acting Insulin Analogs (RAI).

Currently, three such RAIs patents are available, namely, insulin lispro (Humalog®, Lilly Company), insulin aspart (Novorapid ®, Novo Nordisk Company) and insulin glulisine (Apidra®, Sanofi - Aventis Company) [30,31]. These analogs dissociate faster and have quick onset (within 10 – 20 minutes), with shorter duration of action (3 - 5 hours) as compared to soluble insulin (30 - 60 minutes, and 6 – 8 hours, respectively) [32], thus limiting the chance of hypoglycemia 3-4 hours post prandially (after meals) or in post absorptive state. Combination of these insulins with protamine is also available (Novo Mix 30, Humalog Mix50, Humalog Mix25), also known as biphasic insulins [33]. All these RAIs and biphasic mix insulins have been patented to be used in diabetes management by insulin injections for both type-1 and type-2 diabetic subjects.

Discussion

There are several clinical studies which have demonstrated the safety and efficacy of RAI patents in both type-1 and type 2 diabetic subjects, when used with other intermediate acting insulins as a part of " basal bolus" therapy, or as continuous subcutaneous insulin infusion (CSII) in insulin pumps [34]. The time - action profile of RAIs mimics exactly with physiological needs at meal time and controls post-prandial hyperglycemia more effectively and is easily applicable in clinical practice. Furthermore, patient are more compliant to use RAIs at home as compared to soluble insulin which must be injected half an hour before meals and may cause hypoglycemia sometimes after 3-4 hours post meals. In recent clinical trials, RAIs appear to be better than soluble insulins in achieving better glycemic control with less hypoglycemia, both in type-1 and type-2 DM subjects [35].

Regarding Long Acting Insulin Analogs, insulins such as isophane (NPH) and insulin lente can cover the 12 - 24 - hour period with much absorption variability from subcutaneous tissue injection depot [36]. Their pharmacokinetics and pharmacodynamics demonstrate great variabilities after absorption to subcutaneous tissue. Thus they may lead to hypoglycemia especially when peak activity is reached, and when combined with regular insulin, both may additively cause hypoglycemia post meals, e.g., before lunch or late mid night. As in case of RAIs with the applicability of genetic engineering technology, the primary amino acid sequence of insulin molecule can be modified with the change in pH. In addition, insulin first precipitates at injection site and absorbs more slowly and constantly with negligible variability for 24 hours mimicking basal insulin secretion from pancreas [37]. One of the novel insulin is Insulin "Glargine", a long acting insulin up to 24 hours (or even more), with peak less activity, and achieving good glycemic control with less symptomatic hypoglycemia. Efficacy and safety of glargine has been demonstrated by laboratory research and clinical trials as well [38-45]. This insulin glargine is U-100. In the recent years, Glargine U-300 is also available (called Toujeo) with better biological profile and acting up to 36 hours, with more flexibility regarding time of injection. Furthermore, another insulin, comparable to Toujeo, is now also available in the market with the name insulin degludec (Tresiba). These basal insulins have a duration of action of more than 30 hours and provides more flexibility, and are safer and efficacious than older NPH insulins in terms of hypoglycemia reductions and better HbA1c control.

Insulin Detemir is another long-acting insulin analogue that was developed using a different strategy i.e., binding to albumin. This technology has been patented such that aliphatic fatty acid has been acylated to the B29 amino acid with simultaneously removal of B30 amino acid [46]. This results in reversible binding of albumin with the fatty acid acylated to the insulin. Hence, after injection, 98% of the insulin bounds to albumin with gradual release from albumin binding, allowing sustained, prolonged action of insulin detemir. Pharmacokinetic and pharmacodynamic properties and bioavailability of different insulin preparations when injected are presented in Table 1 and graphically in Figure 1.

Preparation	Time of action		
	Onset,h	Peak,h	Effective Duration, h
Short Acting			
Aspart	<0.25	0.5-1.5	2 to 4
Glulisine	<0.25	0.5-1.5	2 to 4
Lispro	<0.25	0.5-1.5	2 to 4
Regular	0.5-1.0	2 to 3	3 to 6
Long Acting			
Detemir	1 to 4	no peak	12 to 24
Glargine	2 to 4	no peak	20 to 24
NPH	2 to 4	4 to 10	10 to 16
Insulin Combinations			
75/25-75% Protamine lispro, 25% lispro	< 0.25	Dual	10 to 16
70/30-70% Protamine aspart, 25% aspart	< 0.25	Dual	15 to 18
50/50-50% Protamine lispro, 50% lispro	< 0.25	Dual	10 to 16
70/30-70% NPH, 30% regular	0.5 to 1	Dual	10 to 16

Table 1: Properties and bioavailability of insulin preparations.

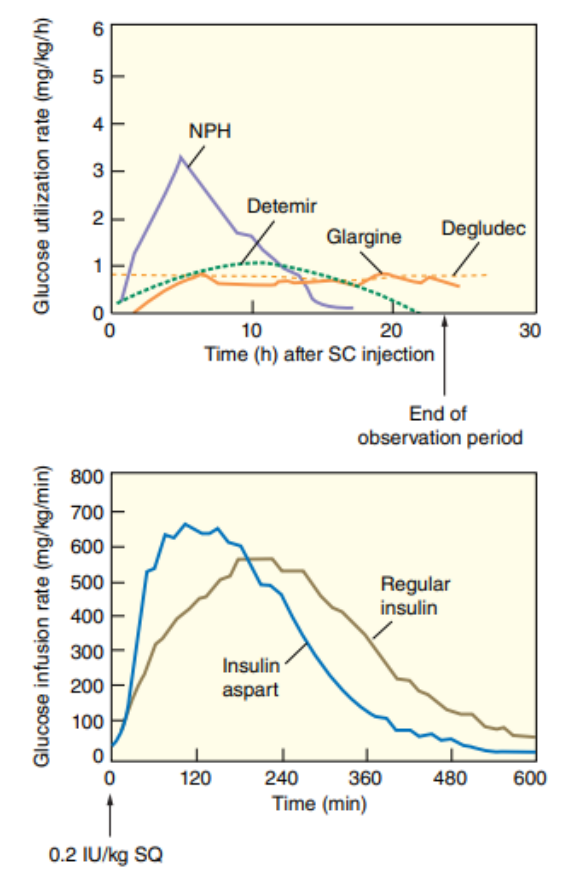

Figure 1: Extent and duration of action of various types of insulin in a fasting diabetic state. (From Gardner DG, Shoback DM. Greenspan's basic and clinical endocrinology. McGraw-Hill Education; 2017).

When injected, insulin detemir is in hexameric form. Thereafter at injection depot site it takes form of hexamer dihexamer equilibrium thus increasing self association state at depot and prolonged duration of action [46]. There is a relative peak activity at 6 to 8 hours after injection (versus peakless activity of glargine) and prolong duration of action up to 24 hours and in dose dependent fashion [47]. Clinical trials have shown less hypoglycemia and less variation in blood glucose levels with insulin detemir as basal insulin in intensive insulin regimens versus NPH insulin [48-50]. Both insulin glargine and levemir, are now approved to be used in diabetic patients [51-53]. RAIs have shortest time action profile, insulins NPH and lente intermediate, while insulin ultra lente, glargine, detemir, tojeo and tresiba have longest duration of action [54-56].

Human insulin analogs produced by genetic engineering and recombinant DNA technology are now most widely used clinically and available commercially in many countries and ultimately has replaced the animal insulins. Insulin is commercially available in unit concentrations of 100U/mL or 500 U/mL, designated U-100 or U-500 respectively. The U-500 with high concentration is used only in rare cases of insulin resistance when the patient requires extremely large doses of insulin to control blood sugar. 100 U/mL is commonly used in most of the countries. Physiologically, insulin secretion basally is low between meals with prandial peaks immediately after meals. As soon as meal is ingested and consumed, insulin is secreted in pulsatile manner accordingly with each meal, with usually no significant secretion overnight and during fasting state.

Considering the management of diabetes in outpatient

clinics, it is highly advisable to prescribe the patient an insulin regimen which mimics the normal physiological insulin release pattern, covering both the prandial and basal requirements, flexible, and that fits best with individual needs and lifestyle. Different regimens are now available and each regimen has different time action profiles and benefits. Patients should be educated about different insulin regimens and their special characteristics. Regimens are designed to meet the daily requirement of insulin in relation with food and basal pattern. Every patient, including adults, children and older age groups, has different eating patterns and different lifestyle. Each patient should be selected specifically for different available insulin regimens. However, basal bolus regimen is the priority if glycemic control is not optimal with conventional regimens. Selection of insulin, e.g., Regular insulin or RAIs, depends on the eating pattern, food density, and other factors as well including physician's clinical experience. RAIs can cover and reduce post meal or postprandial hyperglycemia up to approximately 4 hours. Regular insulin can cover post prandial hyperglycemia up to 6 to 8 hours but may also cause hypoglycemia 3-4 hours post meals, especially in children and lean patients. RAIs should be considered if patients frequently develop day time hypoglycemia, while at work, with regular insulin. Hence, in these settings RAIs are recommended over human regular insulin. Similar is the case with NPH insulin; if patient have hypoglycaemia with NPH, it is preferable to shift the patient to longer acting insulin analogs (insulin detemir, glargine or degludec) [57-64].

Conclusion and Recommendations

In conclusion, it has been demonstrated in the research studies that human insulins (regular and NPH or their combinations such as insulin mixtard 30/70) are not an appropriate option for diabetic patients especially type-1 diabetics; because they are associated with unpredictable pharmacokinetic profiles and also associated with erratic serum glucose values. They may be associated with more day-time, night-time, or late-night hypoglycemia when compared with insulin analogs. Analog insulins are compatible with normal pancreatic physiologic insulin secretion pattern with basal bolus regimens. It is highly recommended to prescribe insulin analogs in clinical practice especially if the patient is type-1 diabetic.

Furthermore, it is recommended to refer the newly diagnosed diabetic patient (after starting the appropriate therapy) to the tertiary care diabetic center for evaluation by diabetologist and diabetes specialist care team for proper management and adjustment of therapy. The diabetic educator and dietitian must be involved in diabetology clinics of tertiary or primary care diabetes centers for education about insulin/ OHA, meal planning, techniques of insulin injections, dosage adjustments according to the meals, SMBG, exercise, sick day management, and management of insulin complications (hypoglycemia, weight gain etc.) and diabetes related complications (neuropathy, retinopathy, nephropathy, foot complications, and others as well).

For type-1 diabetics, it is always advisable and recommended to use basal bolus regimen with available long acting and rapid acting insulin analogs. For type-2 diabetics, they may require combination of insulins with oral agents (such as metformin, DPP-4 inhibitors, SGLT-2 inhibitors, TZDs) [65-68]. However type-2 diabetics may be controlled on simpler mixtures of insulins (Humalog Mix 50, Humalog Mix25, or Novomix 30); if glycemic control is poor, then they can be shifted to basal bolus regimens accordingly. Furthermore, these insulin analogs can be combines as well with GLP1-Receptor Agonists (exenatide, liraglutide, albiglutide, and dulaglutide), which provides good HbA1c control among obese patients with additional reductions of cardiovascular risk factors [69,74].

In conclusive summary, currently available insulin analogues (RAIs, glargine, levemir, degludec) are clinically safer and efficacious for most of the patients as all these insulin analogues mimic physiological insulin release pattern. When combined as basal bolus regimen or MDI, is the best choice for type-1 diabetic patients and most of them type-2 diabetic patients uncontrolled on OHA. Multidisciplinary approach is recommended for the management of diabetes in tertiary care centers, which include diabetologist, endocrinologist, diabetes health educator and dietitian. It is also advisable that all diabetic patients should be screened for diabetes and vascular complications and to initiate appropriate additional therapies with early initiation of insulin to prevent further progress of diabetes related complications.

Conflict of Interest

All authors declare no conflict of interest.

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