Insulin Analogues: Are They Worth in the Management of Type 2 Diabetes Mellitus in Comparison to Human Insulin?

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ABSTRACT
The importance of achieving glycemic goals without compromising patient safety is the main aim of diabetes management. Ever since the discovery of insulin, search for ideal insulin which will mimic normal physiological actions of human insulin still continues. Presently, insulins used are either human insulin or analogue insulin. Commercially available insulins are categorized as rapid-acting, short-acting, intermediate-acting, and long-acting insulins. Long‑acting analogues have a smooth relatively flat 24-hour basal supply with less variability profile as compared to insulin neutral protamine hagedorn (NPH). Rapid‑acting insulin analogues have the advantage of being able to mimic the mealtime insulin response more closely than can injection of unmodified human insulin. However, an argument against use of analogue insulins as compared with use of regular or NPH insulin is one that states that the effectiveness and risk of hypoglycemia are the only two valid clinical outcomes that should be used to compare the analogue and human insulins. So there remains a debate between them with cost effective strategies.

Keywords: Insulin analogues, human insulin, diabetes mellitus, cost effectiveness.

INTRODUCTION
Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. Insulin deficiency in turn leads to chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism. Insulin therapy is important in preventing the adverse clinical effects of the disease. Insulin treatment in type 1 and type 2 diabetes has come a long way since its discovery by Banting and Best in 1921. Insulin is a small protein with long journey with continued research on resolving its complex structure and design super-stable, fast-acting, and cheaper insulin formulations for DM patients.1 Various insulins are now available with respect to time-action profiles, onset, peak, and duration of action. There are also different insulin delivery systems developed, but still the search for ideal insulin which will mimic normal physiological actions of human insulin continues.2-4

The importance of achieving glycemic goals without compromising patient safety has been the main aim of diabetes management since past two decades.5,6 The Diabetes Control and Complications Trial confirmed the link between glycemic control and the complications of diabetes. Therefore, to achieve improved glucose control, the need for new insulin preparations with a faster onset and shorter duration of action and for long‑acting preparations with a more flat time-action profile and less variable bioavailability became apparent in the late 1980s and early 1990s. Thus, innovations for physiological patterns of insulin with different regimens and with different conventional insulin and insulin analogues remain a fundamental component of diabetes management even today.

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STRUCTURE OF INSULIN

The insulin gene is a protein consisting of two separate chains of amino acids, an A and B chain that are held together with sulfide bonds. Amino acids are the basic units that build all proteins. The insulin A chain consists of 21 amino acids and the B chain has 30. The β cells of pancreatic islets synthesize insulin from a single-chain precursor of 110 amino acids termed preproinsulin. In 1980s with the help of recombinant DNA technology, human insulin were discovered which replaced animal insulin. Beef insulin, pork insulin, and beef–pork insulin are no longer commercially available. Human insulin has reduced the adverse effects of animal insulin such as insulin allergy, insulin resistance, and insulin lipodystrophy. Even then the existing conventional human insulins when injected subcutaneously do not match the action profile of normal physiological insulin secretion. Also there is marked inter- and intra-individual variations in pharmacokinetic profile associated with conventional human insulin. Therefore, a change in insulin administration schedule is impossible to eliminate this variability in day-to-day life. Because of all these limitations, there is a need for insulin analogues to mimic the normal physiology. Now currently, insulins used are either human insulin or analogues of human insulin.7

INSULIN JOURNEY

The recombinant DNA technique for human insulin involves the insertion of human proinsulin gene into Saccharomyces cerevisiae (Baker’s yeast) or nonpathogenic laboratory strains of Escherichia coli which serves as production organism. Human insulin is then isolated and purified. Initially the improvements in insulin formulations were limited insulin purity, species, and characteristics of the retarding agent. But, the availability of molecular genetic techniques opened new windows for creating insulin analogues by changing the structure of the native protein and improving its therapeutic properties.8 Modification in insulin molecule structure with the help of recombinant DNA technology has allowed analogues to alter pharmacokinetics since the absorption of insulin gets different from the subcutaneous tissue. Insulin analogues have been engineered to enhance desired molecular properties without altering immunogenicity.9 Second more important is the balance between opinion and evidence. Literature exists on use and comparison of different insulins. The present article attempts to compare human insulin and insulin analogues.

TYPES OF INSULIN

Commercially available insulins are categorized as rapid-acting, short-acting, intermediate-acting, and long-acting insulins. The word designer insulin has been loosely used earlier but it has definite connotation that insulin is designed for a targeted action. Since the introduction of insulin analogues in 1996, these “designer” insulin therapy options have widened. The insulin analogues currently available in the market include rapid-acting analogues (aspart, lispro, and glulisine), long-acting basal analogues (glargine, detemir, and degludec), premixed insulin analogues formulations as Protamine/Lispro (50%/50% and 75%/25%), and Protamine/Aspart (70%/30%). These have been formulated to have a response closer to physiological effects of normal endogenous insulin profile. Long-acting analogues have a smooth relatively flat 24-hour basal supply with less variability profile as compared to insulin neutral protamine Hagedorn (NPH). Rapid-acting insulin analogues have the advantage of being able to mimic the mealtime insulin response more closely than can injection of unmodified human insulin.7,10-12

COMPARISON OF HUMAN INSULIN VERSUS INSULIN ANALOGUES

With advancements and new research, a designer insulin-ultra fast-acting mealtime insulin is launched known as Fiasp (fast-acting insulin aspart). Faster acting insulin aspart is insulin aspart set in a new formulation containing two well known excipients, nicotinamide, and arginine. The excipients result in a stable formulation and faster initial absorption after subcutaneous injection. The result is to create a more physiological insulin profile with a subsequent improvement in postprandial glycemic excursions as compared to conventional insulin aspart.13,14 Following its injection into subcutaneous tissue regular insulin forms hexamers thus slowing its absorption. These hexamers further dissociate into dimers and monomers. Rapid-acting analogues result from changes of aminoacid structure of human insulin. Alteration in aminoacid structure decreases hexameric
insulin formation after injection into subcutaneous tissue leading to a more rapid dissolution to monomers so more rapid absorption with shorter duration of action. The molecular changes do not alter the biological properties of the analogues in terms of binding to the insulin receptor, and the rapid-acting insulin analogues all possess the same glucose-lowering effects as human insulin. While on molar basis, rapid-acting insulin analogues have identical in vivo potency as compared to regular human insulins but higher peak concentrations are achieved. Studies have demonstrated that insulin aspart was absorbed twice as quickly attaining more than double the serum concentrations and rapid taper of metabolic activity compared to regular human insulin. For this reason when converting from regular insulin to rapid-acting insulin analogues, the dose of insulin may need to be reduced. When compared to regular insulin, the rapid-acting insulin analogues lead to less late postprandial hypoglycemia.10-13 The shorter interval for insulin injection premeal (10–15 min) is more convenient and better adherence is noted. All rapid-acting insulin analogues are recommended for an insulin pump.

Many randomized control trials of comparing these insulins in Type 1 diabetes show less severe nocturnal hypoglycemia events with insulin analogues as compared with human insulin, which is attributable to a pronounced difference in the nocturnal pharmacodynamic profile. Beyond HbA1c comparisons, insulin analogues are associated with lower risks of hypoglycemia, lower levels of postprandial hyperglycemia, better patient adherence, greater quality of life, and higher satisfaction with treatment.7-14

HypoAna Trial which compared insulin analogues such as detemir and aspart and human insulin in Type 1 diabetes during their hospital stays showed that there was significant relative risk reduction of 66% nocturnal hypoglycemia compared with human insulin. In the study duration there was severe hypoglycemia observed in 270 [61%] patients receiving human insulin and 171 [39%] receiving insulin analogues. Many studies have shown that for similar A1c levels, nocturnal hypoglycemia was lower in T2DM as compared to T1DM when patients were matched,13,15-17 although among analogues and human insulin there are statistically significant reported differences in hypoglycemia. The study reported that a total of 61% experienced hypoglycemia in patients receiving Human Insulin and a total of 39% experienced hypoglycemia while receiving insulin analogues.17 Study concluded that there was a significant reduction of hypoglycemic episodes in high risk patients in T1DM, who were initiated on analogues insulin as compared to patients taking human insulin.17

The mean difference in HbA1c levels between human insulin and analogues insulin is hardly of any clinical importance. Premixed insulin analogues like protamine lispro and protamine aspartare having an edge over premixed human insulin in improving glycemic status. There are more intraday glucose excursions with premix insulin. Better effectiveness can be seen with premix insulin with just two meals a day and proper timing adherence. With proportions of mixed insulin which are having less physiologic action, so there is an increased risk of hypoglycemia when compared with basal-bolus regimens. Studies have shown that regular insulin and insulin analogues are equally effective during treatment of diabetic ketoacidosis (DKA). The management of DKA with new and recently developed insulin is more safe and efficacious which is published in the most recent studies.10,17

In the transition to the management of DKA after the emergency resolution subcutaneous glargine and glulisine resulted in similar glycemic control but showed a lower rate of hypoglycemia than with NPH and regular insulin. Hence, it is preferred to use basal-bolus regimen over NPH and regular insulin after DKA.18

The intensification of insulin therapy and reaching a goal of <7% HbA1c is not easy. However, the fact remains that fasting plasma glucose, glucose variability, and nocturnal hypoglycemia always occupies the minds of doctors. Two recent Cochrane Reviews which studied the effects of insulin analogue on HbA1c were in favor of insulin analogues in patients with T1DM.19,20 Patients of T2DM showed no significant difference in Hba1c between rapid-acting analogues and human insulin.

Similar pharmacokinetic characteristics were observed when short acting insulin analogues were compared. Traditionally, long-acting insulin analogues have a high rate of variabilities in pharmacokinetic and pharmacodynamics profile. Patients were more adherent and showed a major improvement and treatment satisfaction due to lesser injections, flexibility timings of basal analogues insulin, less fear of dose adjustments, mealtime administration of prandial analogues, lesser pain due to better insulin pens as well as user-friendly injection devices.
With reduced episodes of hypoglycemia to analogues insulin pharmacoeconomics is also highlighted with analogues insulin—as the cost is relatively lowered. Analogue insulins improve treatment satisfaction which will reduce the negative impact of diabetes on quality of life in comparisons with human insulin and NPH. Cost is a major deterrent of analogue insulin in patients adherence; nevertheless, the improvement in satisfaction of the patients is highly significant and it appears difficult to be ignored. Different studies on analogue insulin have shown to increase in quality-adjusted life expectancy. We need to have a more much global assessment of insulin analogues versus regular insulin in terms of cost effectiveness and all the issues which are hard to measure with this complex disease.

The healthcare costs may be relatively similar and may be associated with increases in quality-adjusted life expectancy when we conclude through various studies from across the world. Despite the advances in insulin therapy over the past decade, significant proportions of subjects are not achieving adequate glycemic control even with multiple regimens. The treatment of diabetes is based on individualization and patient’s acceptance and adherence to the treatment protocol. Effective and safe titration of insulin is key for optimal control with long-term and short-term outcomes. Factors, such as hypoglycemic risk, weight, variability, and other comorbid conditions, also have a major impact on diabetes and quality of life.

CONCLUSION

The need for effective insulin therapies is ever increasing since the incidence of DM is increasing tremendously. The amount of insulin needed to treat T2 Diabetes globally is likely to increase by more than 20% by 2030. Two primary concerns of patients are whether an insulin preparation controls their blood glucose adequately without causing hypoglycemia and whether the regimen is simple and convenient. Insulin glargine and insulin detemir offer equivalent glycemic control, with less risk of hypoglycemia, compared with NPH. For the rapid-acting analogues, research efforts are focused on developing molecules that are absorbed into the bloodstream even more quickly after subcutaneous injection. More recent trials of insulin therapy are including measures of patient’s quality of life and cost effectiveness. Insulin glargine and regular human insulin have similar acute stimulatory effects on endothelium-dependent vasodilation in humans. The expectation is that features such as a reduced risk of hypoglycemia and increased convenience will be reflected in improved quality of life scores. The transition pattern is from human insulin to analogues to biosimilars. The story of a perfect insulin is one of a molecule that continues to evolve.

REFERENCES


