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JOURNEY OF INSULIN TILL INSULIN GLARGINE

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Until the discovery of insulin in the 1920s, diabetes mellitus was primarily encountered and perceived as a fatal disease, usually occurring in younger individuals. With the classic work of Banting, Best, and others, however, came the prospect of life-saving insulin replacement therapy, which was quickly pressed into clinical service[1]. Since its discovery and first clinical use in the 1920s, insulin therapy has revolutionized the treatment and natural history of both type 1 and type 2 diabetes mellitus[2]. Historically, in 1890, von Mering and Minkowski1 identified the crucial link between the pancreas and diabetes as evidenced by the diabetic phenotype they induced in dogs after pancreatectomy. Physiologist Sharpey-Schäfer hypothesized that pancreatic islets might produce an "internal secretion" or hormone involved in glucose homeostasis. Consequently, the first 2 decades of the twentieth century witnessed numerous attempts to isolate this internal secretion. Frederick G. Banting conceived of a novel method of isolating the internal secretion by deliberately inducing atrophy of the acinar cells of the exocrine pancreas via duct ligation in dogs, to diminish the potentially destructive effect of digestive enzymes on the islet hormone[3]. In the summer of 1921, assisted by Charles H. Best in the laboratory of John J.R. MacLeod at the University of Toronto, Banting became the first to demonstrate that pancreatic islet extracts consistently reduced hyperglycemia and glycosuria in depancreatized, diabetic dogs[4]. Later that year, with the expertise of biochemist James B. Collip, a novel protocol was developed to purify what they later named "insulin" (Latin: insula, island), from pancreatic islets of whole bovine pancreata without the need for pancreatic duct ligation experiments. The first successful therapeutic use of pancreas extracts of bovine insulin occurred at the Toronto General Hospital on January 11, 1922, on a 14-year-old patient, Leonard Thompson, who was admitted with type 1 diabetes[5]. Such products greatly reduced the incidence of early mortality from diabetic ketoacidosis and completely revolutionized diabetes therapy. In 1923, the Nobel Prize in Medicine and Physiology was jointly awarded to Banting and MacLeod for what is considered one of the greatest advancements in modern medicine[2].

Insulin therapy has significantly evolved since 1922, with major improvements in insulin purification, production, formulation, regimens, and delivery systems. Until the 1980s animal insulins, extracted from either bovine or porcine pancreata, comprised all commercially available insulin formulations. Such soluble, "regular," animal insulin products were initially very impure, leading to immunologic reactions (eg, insulin allergy, immune-mediated lipoatrophy at the injection site, and antibody-mediated insulin resistance) and significant variability in pharmacokinetics and pharmacodynamics. Early advances in purification techniques led to better-quality products with more consistent biological action.[2]. Due to the problem of repetitive injection, subsequent development of newer insulins sought to prolong the time action profile to extend the duration of action and with the goal of reducing the number of daily injections. These longer-acting preparations were designed by combining insulin with zinc and/or basic proteins (protamines) to delay subcutaneous absorption[6]. These formulations included protamine insulin and protamine zinc insulin (PZI) that were developed in the 1930s, isophane neutral protamine Hagedorn (NPH) launched in the 1940s and the trilogy of "lente" insulins introduced during the 1950s. Among the latter, NPH insulin has still retained its clinical utility to this day, as twice-daily insulin, used alone or in conjunction with soluble insulin as a premixed product[2]. It was not until the mid 20th century that further understanding of the natural physiologic insulin secretory pattern leads to the realization that mimicking those patterns was a more appropriate goal of therapy than reducing the number of daily injections. Natural physiologic insulin secretion is characterized by basal insulin release throughout the day, with additional rapid release of insulin in response to carbohydrate ingestion (prandial insulin release)[6]. During the 1950s, Sanger elucidated the primary structure of bovine insulin[7]. Through advances in protein chromatography techniques, the 1970s witnessed the production of highly purified animal insulin, denoted monocomponent or single-peak insulin. Chemically synthesized human insulin was first produced in the 1960s and studied in preliminary clinical trials[2]. In the early 1980s, to overcome the disadvantages of insulin from porcine, bovine, and combinations of both, and to help with the animal source supply problem associated with the increasing incidence of diabetes, biosynthetic insulin was developed using recombinant DNA technology. These insulins were identical in amino acid sequence to human insulin and were first approved by the US Food and Drug Administration (FDA) in 1982[6]. The first recombinant DNA human insulin analog, insulin lispro (Humalog, Eli Lilly, Indianapolis, IN) rapid-acting bolus insulin, was approved by the FDA in 1996, followed by the approval of the basal analog glargine (Lantus; Sanofi-Aventis, Bridgewater, NJ) in 2000. The more predictable action profiles of the long-acting analog insulins (insulin glargine and detemir) are associated with lower rates of hypoglycemia, particularly nocturnal hypoglycemia, than NPH. Less hypoglycemia can also reduce weight gain. These advances, coupled with improvement in both needle devices and insulin delivery systems such as pens, continued to facilitate the use of insulin therapy[6]. In the present day, we now fully embrace the need for insulin products that match the secretion of the endogenous insulin as closely as possible. This journey of insulin is depicted in Fig 1.

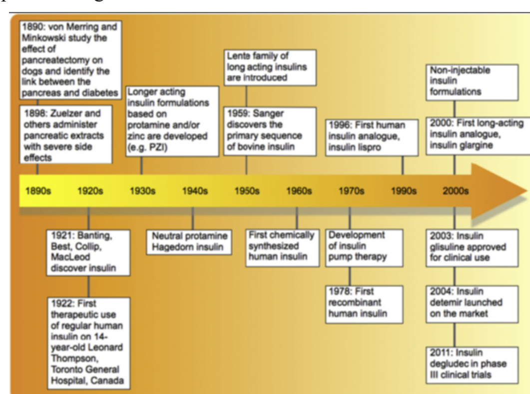

Fig1. The journey of insulin with major landmarks[2]

"In using the insulin it would, of course, be ideal if it could be supplied so as to imitate the natural process."
—J.J.R. Macleod and W.R. Campbell, 1925

This has been the driving force for the search for better and efficacious insulins. Insulin administration is the sole pharmacologic treatment currently available for patients with type 1 diabetes and represents an important therapy for many patients with type 2 diabetes. Unfortunately, despite many important advances in the 90 years since its discovery, physiologic insulin replacement remains an elusive goal. Several epidemiologic studies and clinical trials, including the landmark Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS), the risk of diabetic complications can be prevented and substantially reduced with intensive glycemic control. This is often hindered by patient-related (eg, noncompliance) and treatment-related factors[2]. This has eventually led to the concept of "Basal insulin" i.e maintaining insulin for a prolonged period of time preferably, prandial as well as post-prandial.

The duration of action of regular human (or animal) insulin is 6–8 h when administered subcutaneously, and is thus not sufficient to provide all-night cover, resulting in fasting hyperglycemia. Increasing the dose not only lengthens the time–action profile but also increases the likelihood of hypoglycemia because of its peaked profile[8].

Human insulin is identified as a small protein consisting of chains A (21 amino acid residues) and chain B (30 amino acid residues) linked by two disulfide bonds. The circulating form of insulin is monomeric but highly physicochemically unstable, exogenous insulins are formulated as compact oligomers (mainly hexamers) or even in a crystalline state to ensure sufficient shelf life of the drug product. Human, porcine and bovine insulins exhibit a similar and very complex association pattern in the crystalline state as well as in a solution. Among the prominent factors influencing the association, the state is the presence of zinc ions and phenolic compounds such as phenol or meta-cresol, the ionic strength of the solution, and the insulin concentration. In solution, at low pH (≤3) and in the absence of Zn^{2+} and phenolic compounds, naturally occurring insulin is present as monomers and/or dimmers. Besides, dimers have been observed at high pH and low zinc concentration, while around neutral pH different types of hexamers can form depending on the zinc concentration, the ionic strength and the presence or absence of phenolic compounds[9]. Thus, the development of neutral (porcine) protamine Hagedorn (NPH) insulin in 1946 and the lente (porcine and bovine) series of insulins in the 1950s helped to overcome this limitation by offering prolonged effects due to delayed subcutaneous absorption. A single dose of ultralente or NPH insulin can persist at the site of injection for up to 48 h. However, both of these preparations were associated with substantial pharmacokinetic and pharmacodynamic variability, predominantly due to the fact that the preparations need to be resusp ended prior to administration. However, the protracted subcutaneous absorption of human NPH and human ultralente insulins does not necessarily translate into prolonged bioavailability beyond 24 h. Both the preparations were also found to increase the risk of hypoglycemia, particularly nocturnal hypoglycemia, because of their peak plasma concentrations that occur between 4 and 12 h after the subcutaneous administration. If the dose of ultralente/NPH insulin is markedly reduced, in an attempt to avoid hypoglycemia, the individual may experience the 'dawn phenomenon', whereby there is an insufficient level of insulin to suppress the early-morning increase in glucose output from the liver, resulting in hyperglycemia[8].

Greater understanding of the protein structure of insulin and the roles of key amino acids opened up new avenues for the rational design of insulin analogs with more predictable absorption and time–action characteristics. Initial efforts to prolong the action included a diarginyl-insulin preparation (ArgB31 and ArgB32), and NovoSol Basal (GlyA21, ArgB27, and ThrB30). As hexameric human insulin has to dissociate before absorption into the circulation occurs, certain amino acids are replaced in rapid-acting insulin analogs (B28 in insulin aspart, B28, and B29 in insulin lispro, B3 and B29 in insulin glulisine) to reduce the tendency of self-association allowing a rapid absorption without affecting the insulin-receptor kinetics. After subcutaneous injection and upon dilution with interstitial fluid (two-fold dilution after injection is expected), the non-covalent oligomers of rapid-acting insulin analogs dissociate more rapidly into smaller species which are much faster absorbed than the oligomers[9]. Although, both of these analogs ultimately proved to be unsatisfactory. While human insulin in a Zn^{2+} containing formulation remains almost completely hexameric (Insuman Rapid®, gray in Fig. 2), insulin aspart (in the Novorapid® formulation) and insulin lispro (in the Humalog® formulation) dissociate into monomers within about 20 min. Insulin glulisine (in the Apidra® formulation) dissociates instantaneously under these conditions, triggered not only by the amino acid replacements but also by the absence of the Zn^{2+} ions stabilizing the insulin hexamer, which are present in Humalog® and Novorapid®[9].

Glargine was the first long-acting basal analog to be introduced into clinical practice and differs from human insulin by the replacement of A21 asparagine with glycine and the addition of two arginine residues at B31 and B32 (GlyA21, ArgB31, and ArgB32). These mutations endow glargine with an isoelectric point of 6.4–6.8, implying that it is easily soluble at acid pH and less soluble at neutral pH. As a result, upon subcutaneous injection, glargine forms an amorphous precipitate in the subcutaneous tissue, which slowly dissociates, providing a sustained release of insulin into the circulation. Once injected, glargine is metabolized quickly into two main active metabolites with in vitro activity similar to that of insulin, M1 (GlyA21) and M2 (GlyA21, des-ThrB30). The M1 metabolite accounts for approximately 90% of the daily plasma insulin available. This protracted release of glargine from the subcutaneous depot translates into longer bioactivity than either human NPH or human ultralente insulin. Thus, glargine can be administered once daily, unlike the earlier 'intermediate'/'long-acting' insulin preparations[8]. Compared with previously available intermediate- or long-acting insulin preparations, insulin glargine appears to more closely mimic the action of endogenous basal insulin secretion in healthy individuals with reduced risk of nocturnal hypoglycemia[10].

The EDITION (6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Compared the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus; Both Plus Mealtime Insulin in Patients With Type 2 Diabetes Mellitus With a 6-month Safety Extension Period) series of open-label, noninferiority trials compared the clinical efficacy of glargine U-300 with glargine U-100 in types 1 and 2 diabetes mellitus populations. Glargine U-300 was shown to be consistently noninferior to glargine-100 in these trials when comparing the mean change in hemoglobin A1C, although the U-300 arm frequently required higher doses of insulin to achieve the same glycemic change. Lower incidence of hypoglycemic events, primarily nocturnal, was noted with glargine U-300 compared with glargine U-100. Another interesting observation from these trials was the trend of less weight gain seen in the participants on glargine U-300. As with all new concentrated insulin, glargine U-300 is only available in a prefilled pen calibrated for the higher concentration, so no dose conversions calculations are required. This reduces the potential for dosing errors. Doses are dialed in 1-U increments up to a maximum of 80 U in a single injection[6].

With the advent of follow-on biologic insulins, there is a much-needed potential to reduce diabetes treatment costs and increase the accessibility and variety of insulins available to even those with insurance coverage. The first follow-on biologic insulin was approved by the FDA in 2015 for insulin glargine. Basaglar was approved through an abbreviated new drug application. The preclinical pharmacokinetic/pharmacodynamic studies were clamp studies were done in small populations of healthy subjects and those with type 1 diabetes demonstrated comparable effects with its reference product, glargine U-100 (Lantus). Two-phase III randomized trials compared Basaglar with glargine U-100 (Lantus). One study population had type 1 diabetes and the other population had type 2 diabetes. Both insulin glargine products provided effective and comparable glucose control with similar safety profiles [6]. As a clinician prescribing follow-on biologic insulin, several factors need to be taken into consideration. These are not generic medications and may not perform exactly the same as the parent or the reference product.

CONCLUSION

The last 90 years have witnessed tremendous progress in insulin therapy, from the initial crude, yet life-saving, animal insulin extracts to novel human insulin analogs. To optimize glycemic control in patients with type 1 or 2 diabetes and thus prevent the development and progression of long-term complications, insulin replacement and supplementation strategies must aim to replicate physiologic insulin excursions. Insulin glargine appears to more closely mimic the action of endogenous basal insulin secretion in healthy individuals with smooth absorption without a pronounced peak, prolonged duration of

action, and reduced risk of nocturnal hypoglycemia. With the advent of biological insulin, clinicians need to consider few areas critically, viz., manufacturing process and quality, including batch-to-batch, variability there is no opportunity to monitor their performance because nothing in this area appears in the public domain. Clinicians need to rely on their regulators and the reputation of the manufacturers as to the reliability of the manufacturing and quality monitoring. Post-marketing pharmacovigilance is recommended.

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