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Understanding Insulin Mechanisms, Economic Implications, and Future Prospects

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ABSTRACT
Diabetes, a persistent metabolic challenge affecting various organs,are of three primary types—Type 1, Type 2, and Gestational—stemming from intricate interplays of genetics and environment. On a global scale, 537 million adults grapple with diabetes, with India experiencing a growing burden. The vital role of insulin in glucose regulation involves a complex biosynthesis process. Economic hurdles, compounded by soaring insulin prices, call for policy interventions to ensure accessible healthcare. Diverse insulin types cater to distinct patient needs, while biosimilars, like the FDA-approved Semglee, offer affordability. Economic analyses underscore the advantages of biosimilars, highlighting the dynamic landscape of diabetes management and treatment costs.

Keywords: diabetes, insulin, economics, bio-similars, insulin-analogue, insulin mechanisn, insulin-biosynthesis

I. INTRODUCTION

Diabetes mellitus is a chronic and complex metabolic disorder characterized by elevated levels of glucose in the bloodstream, commonly known as hyperglycemia [1]. Diabetes can affect various organs and systems in the body, leading to complications if not well-managed. It may pose challenges to heart and blood vessels, kidney, eyes, nerves, and gastrointestinal tract.

Type 1 Diabetes (T1D) primarily stems from the immune-mediated destruction of pancreatic β-cells, a process influenced by a combination of genetic and environmental factors. Genetic vulnerability, particularly within the HLA region, affects T cell recognition. Environmental elements such as infections, gut microbiota, and nutrition contribute to shaping the autoimmune response, highlighting the intricate nature of T1D.The screening procedures for Type 1 Diabetes (T1D) are in the initial phases of advancement. Ongoing trials are exploring tests related to insulin, zinc transporter 8, and antibodies targeting islet cells, along with IA-2 and GAD65. It accounts for 5-10% of all diagnosed cases of diabetes. Insulin resistance and beta-cell dysfunction are the hallmarks of type 2 diabetes. Insulin resistance is frequently caused by obesity. An excessive amount of incomplete fat oxidation may aggravate insulin resistance in skeletal muscle and mitochondrial dysfunction, which can result in reactive oxygen species buildup and impaired insulin signaling pathways. Type 2 diabetes is caused by beta-cell failure, which is characterized by a decline in beta-cell mass and a loss of important beta-cell functions. Type 2 diabetes is also influenced by a genetic predisposition to beta-cell dysfunction [2], [3], [4]. Screening for type 2 diabetes can be by either fasting blood sugar, hemoglobin (A1C), glucose tolerance testing, and random plasma sugar. It accounts for 90-95% of all diagnosed cases of diabetes. Gestational diabetes (GDM) predominantly arises from dysfunction in β-cells and chronic insulin resistance throughout pregnancy. The β-cells, which play a crucial role in insulin secretion, experience a decline in their capacity to effectively sense and react to blood glucose levels. This dysfunction, associated with prolonged and excessive insulin production resulting from persistent fuel surplus, is influenced by intricate mechanisms. Insulin resistance, characterized by cells inadequately responding to insulin, exacerbates β-cell dysfunction, leading to diminished glucose uptake and the occurrence of hyperglycemia. This interplay establishes a cyclical pattern characterizing the development of GDM [5].

Diabetes affects 537 million adults globally, or 10.5% of the population between the ages of 20 and 79. By 2030, there are expected to be 643 million more people with diabetes worldwide, and by 2045, that number is expected to rise to 783 million [6]. According to a recent study published in the Lancet, 101 million people in India—or 11.4% of the country's total

population—have been diagnosed with diabetes. Furthermore, a survey conducted on behalf of the health ministry suggests that an additional 136 million individuals, or 15.3% of the population, may have pre-diabetes.

II. INSULIN

Insulin is a polypeptide hormone that consists of 51 amino acids and is essential for metabolism, cell development, and glucose homeostasis. The primary secretors of it are the β cells found in the pancreatic islets of Langerhans. By encouraging the storage of glucose in the muscles, adipose tissue, and liver, insulin regulates blood glucose levels and increases total body weight. It acts through an anabolic pathway in tandem with glucagon to regulate blood glucose levels, whereas glucagon carries out catabolic activities. Through the tyrosine kinase receptor pathway, insulin also promotes the absorption of glucose, glycogenesis, lipogenesis, and the synthesis of proteins in skeletal muscle [7]. Normally, insulin is released in response to the intake of glucose through a mechanism referred to as glucose-induced insulin stimulation. This mechanism includes the internal absorption and metabolic breakdown of ingested glucose[8], [9]. In human β cells, the primary glucose transporters facilitating this process are glucose transporter 1 (GLUT1, encoded by SLC2A1) and GLUT3 (encoded by SLC2A3)[10].

Insulin facilitates the movement of blood glucose into hepatocytes in the liver, where it is further processed into fatty acids, triglycerides, and glycogen. Insulin is also absorbed by adipocytes and skeletal muscles [11]. Through the storage of extra glucose in the liver, this process lowers blood glucose levels. Furthermore, via PI3K/phosphorylation of the Akt/IRS-1 pathway, insulin enhances glycogen synthesis while suppressing hepatic gluconeogenesis, or the synthesis of glucose from non-carbohydrate sources. Insulin also plays a role in controlling blood glucose levels by inhibiting the liver's gluconeogenesis, glycogenolysis, and net glucose synthesis [12]. Insulin aids in the development of new bone and lowers inflammation linked to osteoporosis [13]. It also exerts influences on the central nervous system [14], [15]and performs dual roles with both pro- and anti-atherogenic functions within the vascular system [16].

Mechanism of Action

Insulin is produced by the beta cells located in the Islets of Langerhans within the pancreas, with a higher concentration in the pancreatic head and tail. These beta cells play a vital role in maintaining blood sugar levels by releasing insulin when there is an increase in glucose levels in the blood. Following secretion, insulin interacts with its receptor, the insulin receptor (IR), situated on the target cell membrane. The insulin receptor is composed of four subunits, two α and two β. Upon binding, the α subunits undergo a conformational change, leading to the autophosphorylation of the β subunits, activating the receptor's catalytic function.

This activation initiates a series of intracellular events that regulate metabolic activities, cell growth, and gene expression associated with cell differentiation. The activated insulin receptor phosphorylates insulin receptor substrates (IRS), intracellular proteins crucial for downstream signaling pathways. Tyrosine-phosphorylated IRS serves as binding sites for various signaling partners. Two primary pathways are activated: the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway and the mitogen-activated protein kinase (MAPK) pathway. Akt has diverse roles, including inducing glycogen synthesis, promoting protein synthesis, and enhancing cell survival by inhibiting pro-apoptotic agents. Akt also directly inhibits FoxO transcription factors, which regulate metabolism and autophagy. These pathways, driven by phosphorylated IRS proteins, govern insulin's regulatory roles in cellular function and energy metabolism.

Insulin signaling stimulates growth and mitogenic effects, primarily mediated by the Akt cascade and activation of the Ras/MAPK pathway. Insulin promotes glucose uptake in muscle and adipocytes by translocating GLUT4 vesicles to the plasma membrane. In the liver, insulin inhibits gluconeogenesis by disrupting CREB/CBP/mTORC2 binding.

The PI3K/Akt pathway, activated by IRS, phosphorylates phosphatidylinositol 4,5-bisphosphate to generate phosphatidylinositol 3,4,5-triphosphate, influencing various cellular functions and energy metabolism. Simultaneously, the MAPK pathway, also activated by IRS, oversees cell growth, proliferation, and differentiation in response to insulin signaling [7], [17].

Insulin regulates fatty acid and cholesterol synthesis through SREBP transcription factors, and it promotes fatty acid synthesis by activating USF1 and LXR. A negative feedback loop is provided by Akt, PKCζ, p70 S6K, and the MAPK cascades, leading to serine phosphorylation and inactivation of IRS signaling.

III. ECONOMICS OF DIABETES

In 2021, more than 74 million Indians were diagnosed with diabetes, and this figure is expected to surpass 124 million by 2045. According to the World Health Organization (WHO), around 2% of all deaths in India are linked to diabetes. Alarmingly, an estimated 57% of adults in India, totaling 43.9 million, have undiagnosed diabetes. On average, individuals

dealing with diabetes spend approximately $92 on healthcare, contributing to a total of 1 million deaths directly related to diabetes [18]. Urgent health policy restructuring and increased investment are necessary to optimize healthcare resources amid economic constraints. The financial burden of diabetes treatment affects individuals across all socioeconomic levels, with a recent study in India indicating an average annual expenditure of Rs. 10,000 in urban areas and Rs. 6260 in rural areas for diabetes care [11].

Research on diabetes highlights its widespread direct and indirect cost implications globally. Direct costs encompass both medical and non-medical expenses for individuals and families dealing with diabetes. Meanwhile, indirect costs, affecting society and the government, are linked to decreased productivity. The review underscores that the annual medical costs, both direct and indirect, per patient rise in correlation with the presence of microvascular and macrovascular complications.

A specific study conducted in India between 2008 and 2009 demonstrated that patients without complications incurred total costs of Rs. 4493, while those with complications faced significantly higher costs amounting to Rs. 14,692. This emphasizes the escalating financial burden associated with the increasing severity of diabetes-related complications [18]

IV. ECONOMICS OF INSULIN

The market value of insulin in India is 376.3 million U.S dollars [11]. The annual direct cost of hypoglycemia related to insulin use in Italy is estimated to be €144.7 million. This includes €65 million for severe episodes and €79.6 million for non-severe episodes. Interestingly, the overall cost of hypoglycemia is about 1.7 times higher for Type 2 Diabetes Mellitus (T2DM), amounting to €91.7 million, compared to Type 1 Diabetes Mellitus (T1DM), which totals €53 million [18]. Between 2012 and 2018, the price of available insulin increased by an average of 14% annually. In 2016, insulin accounted for 31% of Type 1 diabetics healthcare costs, up from 23% in 2012.

Insulin prices are soaring due to three main reasons: big companies like Eli Lilly, Novo Nordisk, and Sanofi having too much control, the arrival of expensive insulin analogs, and tricky patent moves. These giants hold a whopping 99% of the market, making it hard for others to compete and keeping prices high. Newer insulin types of also drive-up costs, and crafty patent tactics limit cheaper options. The unclear drug prices and strict rules add to the problem. The solution of these problems could be- push for more generic options, tackle patent issues, improve price talks, be clear about costs, support value-based pricing, and fix the rules to control insulin costs effectively [19].

Market Value

The manufacturing processes utilized to produce regular human insulin and insulin mimics are similar. Insulin glargine costs US$68 757/kg and regular human insulin costs US$24 750/kg. According to estimates, the annual expenses of biosimilars for human insulin were US$48–71 per patient and the analogues were US$78–133 (although detemir was US$283–365) [20].

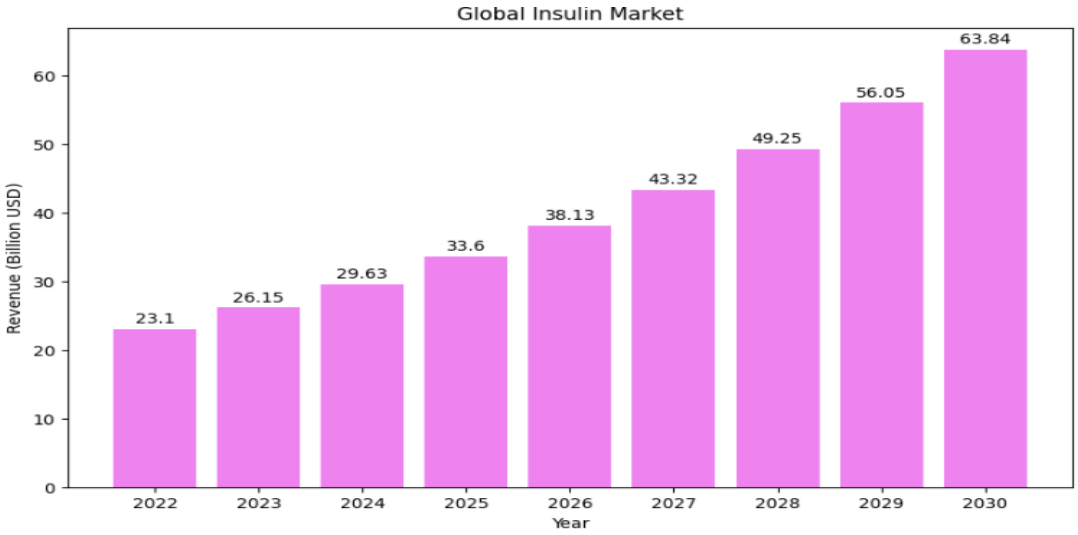

Figure 1: Global insulin market

V. TYPES OF INSULIN

Injecting insulin into the body typically results in the formation of hexameric insulin molecules. To enter the bloodstream through diffusion through interstitial fluid and penetrate into capillary walls, these hexamers must split. As a result, several insulin formulations with varying rates of onset, peak, and period of action have been created to cater to patients' individual demands. The rate at which hexamers splits is altered by these formulations, which also affects the amount of free insulin molecules that enter the bloodstream [21]The next sections provide descriptions of these various forms of insulin formulation.

VI. LONG-ACTING INSULIN

This type of insulin, which is also referred to as basal insulin, maintains a constant amount of insulin production day and night. It is intended to mimic the body's normal basal insulin secretion, which aids in blood sugar regulation. These insulin analogs start acting within two hours, peak action is from six to twenty hours, and its duration of activity is about 36 hours [21].

Insulin Glargine

Insulin glargine was the first long-acting basal insulin analog to be approved for use in clinical practice. It is typically injected subcutaneously once-daily (q.d.) during evening time [22]. Evening administration is frequently used for replicating the body's normal circadian cycle of insulin secretion, which provides coverage throughout the overnight fasting period. There are two changes in glargine's basic structure that set it apart from human insulin. The first change is B-chain's C-terminus receives two arginine residues, raising the isoelectric point from pH 5.4 to pH 6.7 and decreasing the molecule's solubility at the physiological pH of subcutaneous tissue. Second change is neutral glycine residue takes the place of the asparagine residue at position 21 in the A-chain, stabilizing the molecule and preventing dimerization at the acidic pH of 4 [23]. Insulin glargine is a transparent solution, when administered subcutaneously, generates a microprecipitate at the physiologically neutral pH of the subcutaneous region. Insulin glargine provides a reasonably consistent basal insulin supply due to its stability, which causes absorption from the subcutaneous injection site to occur slowly and last for a long time. This behavior is like basal insulin secretion in non-diabetic individuals during the post absorptive state [24].

Insulin Determir

By attaching to insulin receptors, the long-acting, neutral, soluble insulin analogue insulin detemir controls glucose metabolism. Upon injection into subcutaneous tissue, it does not crystallize or precipitate like other insulin do. At the injection site, hexamers are formed by insulin detemir. The solubilized formulation is able to stay in the depot long enough to bind to albumin after the insulin separates into dimers and monomers before to being absorbed into the bloodstream [25]. Two possible mechanisms that may be involved in the prolonged effect of detemir are the reversible binding to albumin and the delayed absorption as a result of self-association. It is therefore possible that two different "buffering" mechanisms contribute to both reduced injection-to-injection variability and a longer period of action. The latter was thought to be the reason for the compound's prolonged retention in subcutaneous tissue, which led to the establishment of albumin binding in the interstitial space. Because detemir is 98% bound to albumin in circulation, the pace at which blood is transported to interstitial fluid is slowed down [23].

VII. INTERMEDIATE ACTING INSULIN

As the name suggests, it has a duration between rapid and ultra-long acting insulin. Intermediate acting insulin analogs have an onset of action around 1-2 h, peak action of 6-10 h and activity duration of 10-16 h [21].

NPH Insulin

NPH insulin, which is insoluble, is produced when zinc and insulin cocrystallize at an isophane ratio and neutral pH in the presence of protamine, a basic polyarginine peptide. It is unknown how precisely the insulin-protamine combination binds. The nature and form of the precipitate, as well as divalent ions like zinc and other additional ligands like protamine and phenolic derivatives, all contribute to the delayed release of insulin from the precipitated NPH insulin crystals following subcutaneous injection. Nevertheless, it is unknown exactly how NPH insulin dissociation occurs [26]. A syringe, insulin pen, or insulin pump can be used to provide NPH insulin, which is often injected subcutaneously, or beneath the skin. Protamine, a basic peptide that co-crystallizes with insulin in NPH formulations, is often extracted from the sperm of Salmonide fish. Protamine derived from Chum Salmon (Oncorhynchus keta) is a blend of four arginine-rich peptides with a molecular weight

of approximately 4 kDa [27]. NPH insulin stimulates the liver to support hepatic glycogen production and fatty acid metabolism for lipoprotein formation. It encourages the production of protein and glycogen in skeletal muscles. It aids in the creation of triglycerides in adipose tissue and controls lipolysis by blocking triglyceride hydrolysis. It promotes the uptake of ions like potassium, magnesium, and phosphorus into cells by making the cell membrane permeable [28].

VIII. SHORT ACTING INSULIN

Short acting insulin(Bolus or mealtime insulin) begins working in 30 to 40 minutes, peaks at 1.5 to 2 hours, has quicker onset of action typically within 0.5-1 hour, surpassing that of regular insulin. and lasts 6 to 8 hours [29], [30].

Individuals with diabetes commonly use this 20-30 minutes before meals,these insulins align with carbohydrate metabolism, ensuring optimal activity during sugar and starch absorption, effectively preventing blood sugar spikes as there is importance of consuming food within 30 minutes to avoid potential low blood sugar levels (hypoglycemia) [21], [30].

Short-acting insulin analogs, when injected subcutaneously, initially form hexamers, slowing absorption over time, these hexamers break down into smaller units, causing a delayed onset of action [31].

Examples include Actrapid, Humulin, Hypurin, and Neutral [21].

These are utilized independently in insulin pump, commonly integrated with other insulin types for comprehensive blood sugar management. Short-acting insulin is offered in two primary brands: Actrapid and Humulin S. Both formulations contain 100 units of insulin per milliliter and are presented in various formats. [32].

Cartridges, reusable insulin pens, provide a convenient and portable insulin injection method. In contrast, vials hold liquid insulin and necessitate separate syringes or insulin pumps for administration [32], [33].

Short-acting insulin injections may lead to local side effects like itching, redness, pain, bleeding, or bruising at the injection site. Over time, lipohypertrophy, the development of fatty lumps under the skin, can occur. Infrequently, temporary vision changes may result from blood sugar fluctuations.The most serious side effect is hypoglycemia, causing sweating, dizziness, shakiness, and, in severe cases unconsciousness [21].

Storage and Handling

Refrigerate unopened vials or cartridges (2°C to 8°C or 36°F to 46°F) until first use, avoiding freezing. Once opened, store at room temperature (up to 25°C or 77°F) for up to 28 days. Discard after this period, regardless of remaining insulin. Shield insulin from light and heat, avoiding direct sunlight and extreme temperatures [33].

IX. RAPID-ACTING INSULIN

Rapid-acting insulin analogs, to emulate the body's natural insulin response to meals, are ideal for pre-meal blood sugar control in diabetes. With a quick onset (5-15 minutes) and a duration of 4-5 hours, they effectively counteract post-meal glucose surges, mimicking the body's response. Peak action is at 30-90 minutes which aligns well with the typical post-meal blood sugar peak, optimizing blood sugar control and minimizing the risk of hypoglycemia between meals [21], [34].

The advantages of rapid-acting insulin analogs is from subtle adjustments to the insulin molecule. Through strategic alterations of one or two amino acids at specific locations, they have a modified structure. Unlike regular insulin, which forms slow-absorbing clusters of six molecules (hexamers), the altered structure of analogs prevents cluster formation. This enables individual insulin molecules to enter the bloodstream more quickly, ensuring rapid action. These modifications do not significantly impact how insulin interacts with cells, preserving its effectiveness in regulating blood sugar levels.[30] Rapid-acting insulins can be administered using a traditional syringe or a disposable pen preloaded with up to 300 U of insulin. Despite the convenience of pens, they are of higher costs [35].

Examples of Rapid-Acting Insulin

Lispro operates by exchanging the positions of two amino acids, proline and lysine, in its B chain.Whereas Aspart achieves a quicker onset of action by substituting aspartic acid for proline at a specific position, facilitating swift action [21].

Pre-mixed insulin simplifies the management of multiple insulin types, combining rapid-acting and intermediate-acting insulin in a single injection. It starts working within 5-60 minutes, ensuring extended blood sugar control for 10-16 hours [29].

X. INSULIN BIOSYNTHESIS

From Gene to Hormone

Insulin, a crucial hormone for blood sugar control, undergoes a fascinating process called insulin biosynthesis within pancreatic beta cells before entering the bloodstream. This complex sequence involves a highly coordinated interaction among diverse cellular elements [36].

The genetic information for insulin production is stored in DNA within the cell nucleus. Transcription in the nucleus converts the insulin gene's DNA sequence into mRNA, which moves to the cytoplasm for translation. Ribosomes in the cytoplasm interpret mRNA to create preproinsulin, which undergoes modifications in the endoplasmic reticulum (ER). The ER facilitates folding and disulfide bond formation, transforming preproinsulin into proinsulin.

Proinsulin then moves to the Golgi apparatus for further processing, becoming secretory vesicles. In the Golgi, prohormone convertase enzymes cleave proinsulin into insulin and C-peptide. These vesicles release insulin and C-peptide into the bloodstream through exocytosis, completing the insulin biosynthesis process. The released insulin circulates throughout the body, regulating blood sugar levels [37], [38].

Human Insulin Analogues

Synthetic insulins designed to mimic the body's typical insulin release pattern. However, they contain slight structural or amino acid modifications that give them distinct qualities when injected.
Eg: Glulisine, Aspart, Lyspro [39].

Biosimilar Insulins

Any product that has a high degree of structural similarity with a biological medication, such as insulin, and shows no relevant change from the original product [40].

For those with type 1 diabetes, biosimilar insulins may be a beneficial choice. Since their release onto the market, the price of insulin has decreased both locally and globally, improving accessibility for payers as well as patients. Eventually, biosimilar insulins will make insulin therapy more widely available and provide diabetics more options for treatment. However, some of these benefits of biosimilar insulins will be lost if reference biologic insulins are no longer available or available in addition to biosimilar insulins [41].

The FDA approved Semglee, the first insulin biosimilar, in July 2021. Semglee is a long-acting insulin analogue that functions similarly to Lantus (insulin glargine) and can be used interchangeably [42].

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