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Is Insulin A Miracle Medicine and A Life-Saving Breakthrough for Diabetic Patients?

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ABSTRACT

Insulin is a medical miracle and a life-saving breakthrough for diabetic patients, especially those with Type 1 diabetes, as it turns a fatal condition into a manageable one. While it is not a cure, it acts as an essential, life-sustaining hormone replacement that controls blood glucose levels and prevents imminent death. **Insulin** is a pharmaceutical preparation of the protein hormone used to treat high blood glucose. Such conditions include type 1 diabetes, type 2 diabetes, gestational diabetes, and complications of diabetes such as diabetic ketoacidosis and hyperosmolar hyperglycemic states. Insulin is also used to treat hyperkalemia. Typically, it is given by injection under the skin, but some forms may also be used by injection into a vein or muscle. Insulin can be made from the pancreas of pigs or cows. Human versions can be made either by modifying pig versions or recombinant technology using mainly *E. coli* or *Saccharomyces cerevisiae*.

Keywords : *Saccharomyces cerevisiae*, Diabetes mellitus (DM), PI3K-Akt Pathway, Growth hormone-releasing hormone (GHRH), Double diabetes

INTRODUCTION

An assortment of prevalent endocrine disorders characterized by persistently elevated blood sugar levels is collectively called diabetes mellitus (DM) (1).

Disruptions in the processing of insulin, defects in insulin receptors, or issues occurring after receptor activation can result in CNS issues, including AD, Parkinson's disease, Huntington's disease, various malignancies, migraine headaches, and schizophrenia (2).

Type 1 typically manifests in youth, while type 2 is commonly associated with adults who have prolonged elevated blood sugar due to lifestyle and dietary factors (3).

Type 2 diabetes (T2D), which is characterized by hyperglycemia, is emerging as a leading health challenge; the cases remain undiagnosed. (4)

Etiopathogenesis of T2D is multifactorial, involving the interaction of both genetic and environmental factors (5).

Research over several decades has been dedicated to understanding the secretory mechanisms of the insulin-producing pancreatic β-cells and has resulted in the development of several new glucose-lowering medications, including incretin-based drugs (6,7).

However, the neighboring α-cells, which produce the 29–amino acid peptide hormone, glucagon, are now receiving increasing clinical interest (8).

Diabetes mellitus (DM) is currently a major social and economic burden worldwide. The global epidemic proportion of DM is one of the most important health problems of the 21st century, being the cause of four million deaths in 2017 (9).

Inflammation initially targets peripheral tissues specialized in metabolism, such as the liver, adipose tissue, and pancreatic islets, and it plays a key role in insulin resistance and β-cell dysfunction.(10,11).

T2DM is a progressive metabolic disorder classically defined by chronic hyperglycemia due to the combination of an abnormal insulin secretion by pancreatic islet β-cells and increased insulin resistance of insulin-target tissues (adipose tissue, skeletal muscle, liver, and brain) (12).

Guidelines for T2DM management include, as first-line therapy, serious lifestyle interventions such as physical Exercise, while long-term add-on therapies include medication to increase insulin secretion and sensitivity (13).

Although these treatments are adequate to improve hyperglycemia, they alleviate symptoms rather than target the root cause of the disease, and lead to the development of secondary complications (14).

In recent years, the CNS has gained much interest as a key regulator ofglucose/energy homeostasis. T2DM is not only caused by failures in pancreatic β-cells but also dysfunctions in the CNS that could lead to the development of this disease (15).

Glucose is a crucial energy source for the body; therefore, its circulating levels must bewithin an adequate range to meet the metabolic demands and ensure the proper functioning of the entire body. Failure in this glucose- The sensing/regulation process leads to metabolic disorders, including T2DM. The pancreatic β- and α-cells are key elements in the process of glucose sensing and homeostasis (16).

Glucagon increases glucose levels, while insulin decreases them. It is probably theratio of these two hormones that best determines hepatic glucose production, although the relative role of the two hormones in diabetic hyperglycemia is still debated (17).

Research has found that endocrine cells in the digestive system have a unique role in regulating islet function. Hormones secreted by intestinal L cells, such as GLP-1, and by K cells, such as GIP, can exert incretin effects on the islets.(18)

The discovery of intestinal incretins such as glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide(GIP) has laid the groundwork for the dialogue between the intestine and pancreatic cells.(19,20)

Pancreas – Anatomy

The pancreas is a retroperitoneal organ located in the upper abdomen, spanning from the duodenum to the spleen. It is divided anatomically into the head, neck, body, and tail.(21)

The islets are composed of multiple cell types with distinct roles: alpha (α) cells secrete glucagon; beta (β) cells produce insulin; delta (δ) cells release somatostatin; PP cells produce pancreatic polypeptide; and epsilon (ε) cells secrete ghrelin Beta cells are located centrally in the islets and are the main regulators of glucose homeostasis via insulin production.(22)

Insulin Structure Insulin is a peptide hormone composed of two chains: the A chain (21 amino acids) and the B chain (30 amino acids), connected by disul de bonds. It is initially synthesized as preproinsulin, which is converted to proinsulin in the endoplasmic reticulum and then cleaved into insulin and C-peptide in the Golgi apparatus. The mature insulin molecule is stored in secretory granules within pancreatic beta cells.(23,24)

Glucose enters beta cells via GLUT2 transporters and is metabolized, thereby increasing the ATP/ADP ratio. This rise causes ATP-sensitive potassium channels to close, depolarizing the cell membrane and opening voltage-gated calcium channels (25).

Additional stimuli include amino acids, fatty acids, incretins like GLP1, and parasympathetic neural activity (26).

Insulin Signaling Pathway.

After entering circulation, insulin binds to its receptor, a heterotetrameric complex composed of two α and two β subunits. Ligand binding induces autophosphorylation of the β subunits' tyrosine residues, initiating the signaling cascade (27).

PI3K-Akt Pathway

The phosphorylated insulin receptor recruits insulin receptor substrates (IRS), especially IRS-1 and IRS-2, which undergo further tyrosine phosphorylation. These IRS proteins activate phosphoinositide 3-kinase (PI3K), converting membrane PIP2 to PIP3 (28).

PIP3 then activates PDK1, which in turn activates Akt (also known as Protein Kinase B). Activated Akt promotes: Translocation of GLUT4 transporters to the cell membrane in muscle and adipose tissues, increasing glucose uptake. Inhibition of glycogen synthase kinase 3 (GSK-3), enhances glycogen synthesis. Suppression of gluconeogenesis in hepatocytes.

MAPK Pathway

In parallel, insulin signaling also activates the MAPK (mitogen-activated protein kinase) pathway via Grb2 and Sos proteins, leading to cell proliferation and differentiation (29).

This branch of the pathway is particularly relevant in mitogenic and growth responses. Defects at any stage of this signaling cascade can contribute to insulin resistance, a hallmark of type 2 diabetes mellitus (30).

The hypothalamus; AKey Regulatory Site in Glucose Homeostasis.

The brain, mainly the hypothalamus, integrates these gut-derived signals, along with others, to coordinate the regulation of food intake, energy expenditure, and glucose homeostasis (31,32).

Accumulating evidence in recent decades suggests that disruption of glucose-sensing mechanisms in the hypothalamus is intimately involved in the pathogenesis of obesity and T2D (33,34).

The hypothalamus plays a critical role in maintaining glucose homeostasis by regulating the pancreatic release of insulin and glucagon through its control over both branches of the autonomic nervous system (35).

The sympathetic nervous system stimulates the release of the hormone epinephrine from the adrenal glands. Epinephrine, in turn, stimulates the pancreas to release glucagon, which stimulates the release of stored glucose from the liver, leading to increased blood glucose levels (36).

Hypothalamus, acting through the parasympathetic nervous system, stimulates the release of insulin from the pancreas. The resulting increase in insulin functions to lower blood glucose levels by promoting the uptake of glucose by cells and tissues throughout the body, including skeletal muscle, liver, and adipose tissue (37).

The hypothalamus also indirectly regulates the pancreas through the release of growth hormone-releasing hormone (GHRH), which stimulates the release of insulin, and somatostatin, which inhibits the release of glucagon (38).

Recent research has demonstrated that circulating signalling factors, including glucose, insulin, and leptin, can regulate many hypothalamic neuronal populations to exert significant effects on the regulation of blood glucose, food intake, energy expenditure, and adiposity in both genetically predisposed and diet-induced T2D in animal models (39).

Differences between Type--1 and Type--11 Diabetes

Diabetes mellitus represents a group of physiological dysfunctions characterized by hyperglycaemia resulting directly from insulin resistance (in the case of type 2 diabetes mellitus—T2DM), inadequate insulin secretion/production, or excessive glucagon secretion (in type 1 diabetes mellitus—T1DM) (40).

Type 1 diabetes is a chronically progressive autoimmune disease that affects approximately 1% of the population in the developed world (41).

This adverse immune response is induced and promoted by the interaction of both genetic and environmental factors. In contrast, in type 2 diabetes, insulin resistance coupled with reduced insulin output appears to be the major cause of hyperglycaemia (affecting approximately 8.5% of the adult population) (42).

Although the aetiology of diabetes may differ from T1DM to T2DM, common features may occur during the progression of the disease. In the case of T2DM (insulin resistance), pancreatic β-cell failure may occur in the long term, while in T1DM (pancreatic β-cell death/insulin deficiency) insulin resistance can be induced as the condition progresses (43).

Thus, similarly to both types of diabetes, particularly in the long term, insulin resistance and β-cell dysfunction/death may be present, impairing several tissues and cell function and metabolism.(44)

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Hyperglycaemia, dyslipidaemia, and low-grade inflammation (consisting of circulating inflammatory cytokines or adipokines released by adipocyte expansion (45)

Gut microbiota dysbiosis is considered an important factor in the progression of T2DM and is generally present in obese individuals who are at risk of T2DM (46).

These conditions lead to β-cell stress and insulin resistance (through a variety of processes that mainly include uncontrolled generation of reactive oxygen and nitrogen species (ROS/RNS) and cytokine-dependent signals) (47).

Insulin resistance is also prominent in patients with T1DM and involves hepatic, muscle, and adipose tissues (48).

Weight gain caused by the administration of exogenous insulin, together with the adoption of a sedentary lifestyle (particularly related to a fear of exercise-induced hypoglycaemia.(49)

A high-calorie diet leads to changes in an individual's body composition, lipid profile, and blood pressure, similar to those observed in metabolic syndrome in obesity. (50,51)

People with T2DM generate insulin resistance and an increased risk of cardiovascular disease [52].

The presence of metabolic syndrome in patients with TDM1 results in the phenotype called "double diabetes" (53).

Individuals with T1DM and T2DM share several cardiometabolic complications, such as endothelial dysfunction, changes in glomerular filtration/kidney function, low-grade inflammation, oxidative stress, blood coagulation, mitochondrial dysfunction, cardiac dysfunction, anabolic resistance, metabolic inflexibility, and gut microbiota dysbiosis (54).

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Insulin types

Insulin types are classified by how fast they work, when they peak, and how long they last. Main types include Rapid acting (5-20 minutes onset), Short acting (30-45 minutes onset), Intermediate acting (1-4 hours onset), Long acting (1-2 hours onset,--24 hrs duration), and mixed (Combinations). They are used to manage blood sugar, often in combination. The beta cells present in our pancreas are responsible for producing insulin, which helps in using and storing the glucose present in our body that comes from the carbohydrates we consume in our diet. Glucose circulates in our bloodstream and is a necessary element for performing various body functions, and is also utilized by different cells for producing energy..When our body becomes incapable of producing enough insulin, as it happens in the case of type 1 diabetes, or acts resistant in proper usage of insulin, as it happens in the case of type 2 diabetes, the cells in our body do not have access to the energy they actually require. On the other hand, the glucose levels in our bloodstream start increasing, which can result in some severe consequences. Thus, it becomes imperative to use manufactured insulin to gain control over blood sugar levels.

Basal insulin

It is similar to the insulin our bodies make all day and night naturally. It helps keep our glucose levels steady when we're not eating, like between meals and while we sleep. Think of it as the "cruise control" for glucose. Basal insulin is usually taken once or twice a day and works slowly over a long time. Commonly prescribed basal insulins include Levemir, Lantus, and Tresiba.

Common Basal Insulin Examples (Long-Acting Analogues)

- **Insulin Glargine (U-100):** Lantus, Basaglar, Semglee, Rezvoglar (24-hour duration).
- **Insulin Glargine (U-300):** Toujeo (concentrated, often lasting >24 hours).
- **Insulin detemir:** Levemir (lasts 16–24 hours).
- **Insulin decudec:** Tresiba (ultra-long-acting, lasts 42+ hours)

Bolus insulin

It is the insulin we take to cover the sugar from the food we eat and lower glucose when it gets above the target range. It's like the "booster" that helps manage the rise in blood sugar after meals. Bolus insulin works quickly and is usually taken right before meals. It helps prevent our glucose from getting too high after we eat.

Rapid-Acting Bolus Insulin Examples

- **Insulin Lispro:** Humalog, Admelog, Lyumjev
- **Insulin Aspart:** NovoLog, Fiasp (faster acting), Trurapi
- **Insulin Glulisine:** Apidra
- **Inhaled Insulin:** Afrezza (technically rapid-acting)

Why are both basal and bolus insulin important

Basal insulin keeps blood sugar levels steady throughout the day and night, while bolus insulin helps manage the spikes in blood sugar that happen when we eat. Together, they help people with diabetes keep their glucose levels in a target range. Both basal and bolus insulin are vital for people with Type 1 diabetes, while a person living with Type 2 or gestational diabetes may need only basal or both basal and bolus.

How Can Insulin Be Taken?

Insulin is usually taken with the help of an insulin syringe. There are marked lines on the syringe that indicate the amount of medication, and a person with diabetes can self-administer the quantity of insulin taken as per the prescription of the doctor and use the same as per the doctor's instructions. Besides injecting insulin, here are a few other options that can be used for taking insulin:

Insulin pens

- Jet injection
- Insulin pumps
- Inhaled insulins

Inhaled insulin arrives in India to tackle 'needle phobia.'

This rapid-acting inhaled insulin, recently introduced in India under the name Afrezza, is said to offer an important alternative for selected patients who are otherwise reluctant to start insulin therapy."Fear of injections remains a major reason for delaying insulin therapy, even when it is clearly required. This hesitation, often referred to as insulin inertia, is an important cause of poor **blood sugar** control and can increase the risk of long-term complications," noted Dr Milind Patil, assistant professor, Department of Endocrinology, DPU Super Specialty Hospital, Pimpri, Pune. Can't my diabetes be managed without insulin injections?' This is one of the most common questions patients ask when doctors discuss starting insulin. "Fear of injections remains a major reason for delaying insulin therapy, even when it is clearly required. This hesitation, often referred to as insulin inertia, is an important cause of poor **blood sugar** control and can increase the risk of long-term complications," noted Dr Milind Patil, assistant professor, Department of Endocrinology, DPU Super Specialty Hospital, Pimpri, Pune.For many patients, the needle itself becomes a psychological barrier between insulin and effective treatment. Although modern insulin needles are very small and cause minimal discomfort, anxiety related to injections is common. "This often leads to missed doses or complete avoidance of insulin," explained Dr. Patil. (55)

Conclusion

Insulin is a hormone that lowers the level of glucose in the blood. It's made by the beta cells of the pancreas and released into the blood when the glucose level goes up, after eating. Insulin helps glucose enter the body's cells, where it can be used for energy or stored for future use. Insulin is a medication used in the treatment and management of diabetes mellitus type-1 and sometimes diabetes mellitus type-2, both of which are significant risk factors for coronary artery disease, stroke, peripheral vascular disease, and a host of other vascular conditions.

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