



INSULIN AND ITS ROLE IN DIABETES MELLITUS

Irkinjanova Fayzixon

University of Business and Science, Department of Therapeutic Work
24_05 group students

Sobirov Olimjon Odiljonovich

Scientific advisor:

<https://doi.org/10.5281/zenodo.15488653>

Abstract: Diabetes mellitus, a global health crisis characterized by chronic hyperglycemia, affects over 500 million individuals, driving significant morbidity and mortality. Insulin, a peptide hormone secreted by pancreatic beta cells, is pivotal in regulating glucose homeostasis and managing diabetes. This article provides an exhaustive exploration of insulin's biochemical structure, molecular mechanisms, and therapeutic applications in type 1 and type 2 diabetes. It examines insulin's biosynthesis, signaling pathways, and the pathophysiology of insulin deficiency and resistance, while highlighting cutting-edge advancements in insulin therapy, including recombinant analogs, smart delivery systems, and regenerative approaches. Challenges such as hypoglycemia, weight gain, patient adherence, and global access disparities are critically analyzed. By synthesizing contemporary scientific evidence, this article underscores insulin's indispensable role in mitigating diabetic complications, enhancing quality of life, and addressing the escalating diabetes epidemic.

Keywords: Insulin, diabetes mellitus, glucose homeostasis, insulin resistance, insulin therapy, hyperglycemia, beta cells, recombinant insulin, type 1 diabetes, type 2 diabetes, continuous glucose monitoring, insulin analogs.

Diabetes mellitus, encompassing type 1 and type 2 forms, stands as a formidable global health challenge, with prevalence surpassing 500 million cases and projections estimating further escalation by 2045. Defined by persistent hyperglycemia, diabetes results from impaired insulin production, action, or both, leading to devastating complications including cardiovascular disease, diabetic retinopathy, nephropathy, neuropathy, and lower-limb amputations. The discovery of insulin in 1921 by Frederick Banting and Charles Best marked a transformative milestone, converting a once-lethal condition into a manageable chronic disease. Insulin, a 51-amino-acid peptide hormone, orchestrates glucose, lipid, and protein metabolism, serving as the linchpin of metabolic homeostasis. Its role extends beyond glycemic control to influence cellular growth, differentiation, and energy storage, making it indispensable in both physiological and pathological contexts. This article offers an in-depth examination of insulin's biochemical properties, physiological mechanisms, and





therapeutic significance in diabetes management, emphasizing its critical role in type 1 and type 2 diabetes, while addressing current challenges and future directions in insulin-based therapies. By integrating molecular insights, clinical advancements, and public health perspectives, it aims to elucidate insulin's enduring importance in combating the diabetes epidemic.

Insulin is encoded by the INS gene on chromosome 11 and synthesized in pancreatic beta cells within the islets of Langerhans. The biosynthetic pathway begins with preproinsulin, a 110-amino-acid precursor, which is cleaved in the endoplasmic reticulum to yield proinsulin. Subsequent enzymatic processing by prohormone convertases (PC1/3 and PC2) and carboxypeptidase E in the Golgi apparatus produces mature insulin, comprising A (21 amino acids) and B (30 amino acids) chains linked by two disulfide bonds, with an intrachain disulfide bond stabilizing the A chain. Insulin secretion is a tightly regulated process triggered by glucose metabolism. Glucose enters beta cells via GLUT2 transporters, undergoes glycolysis and oxidative phosphorylation, and increases the ATP/ADP ratio. This closes ATP-sensitive potassium channels (KATP), depolarizing the beta-cell membrane and opening voltage-gated calcium channels. The resultant calcium influx stimulates insulin granule exocytosis. Other stimuli, including amino acids, incretin hormones (e.g., GLP-1), and vagal nerve activation, amplify insulin release, ensuring precise glycemic control.

Upon secretion, insulin exerts its effects by binding to the insulin receptor, a transmembrane tyrosine kinase. Receptor autophosphorylation activates downstream cascades, primarily the phosphatidylinositol 3-kinase (PI3K)-Akt pathway, which promotes glucose transporter 4 (GLUT4) translocation to the plasma membrane in skeletal muscle and adipose tissue, facilitating glucose uptake. Simultaneously, insulin inhibits hepatic gluconeogenesis and glycogenolysis by suppressing key enzymes (e.g., PEPCK, G6Pase) and promotes glycogenesis and lipogenesis via activation of glycogen synthase and acetyl-CoA carboxylase, respectively. In non-classical tissues, such as the brain and endothelium, insulin modulates neuroprotection and vascular function, highlighting its pleiotropic roles. Dysregulation of these processes underpins diabetes pathophysiology.

Type 1 diabetes, affecting 5-10% of diabetic patients, results from autoimmune destruction of beta cells, mediated by T-cell infiltration and autoantibodies targeting glutamic acid decarboxylase (GAD65), insulin, and islet antigen-2 (IA-2). Genetic predispositions (e.g., HLA-DR3/DR4 haplotypes) and environmental triggers, such as coxsackievirus infections, contribute to beta-cell





loss, leading to absolute insulin deficiency. Patients develop severe hyperglycemia, weight loss, and diabetic ketoacidosis (DKA), a life-threatening condition characterized by ketone accumulation and acidosis. Lifelong exogenous insulin therapy is essential to prevent DKA and maintain metabolic stability. In contrast, type 2 diabetes, comprising 90-95% of cases, is driven by insulin resistance, where target tissues exhibit diminished responsiveness to insulin, often compounded by progressive beta-cell dysfunction. Insulin resistance is multifactorial, involving visceral obesity, chronic inflammation, and genetic variants (e.g., TCF7L2 polymorphisms). Elevated free fatty acids, TNF- α , IL-6, and resistin impair insulin signaling by inducing serine phosphorylation of insulin receptor substrate-1 (IRS-1), disrupting PI3K-Akt activation. Initially, beta cells compensate with hyperinsulinemia, but chronic glucolipotoxicity and endoplasmic reticulum stress precipitate beta-cell apoptosis, reducing insulin secretion and exacerbating hyperglycemia.

Insulin therapy is the cornerstone of type 1 diabetes management and a critical intervention in advanced type 2 diabetes. The development of recombinant human insulin in the 1980s, using *Escherichia coli* and yeast expression systems, eliminated reliance on animal-derived insulin, reducing immunogenicity and improving supply. Insulin analogs, engineered through amino acid substitutions, mimic physiological insulin profiles more effectively. Rapid-acting analogs (e.g., lispro, aspart, glulisine) exhibit faster onset and shorter duration, ideal for postprandial glucose control, while long-acting analogs (e.g., glargine, detemir, degludec) provide stable basal insulin levels, minimizing nocturnal hypoglycemia. Delivery systems have evolved significantly, with insulin pens offering dosing precision and portability, and insulin pumps enabling continuous subcutaneous insulin infusion (CSII) with programmable basal and bolus doses. Continuous glucose monitoring (CGM) systems, integrated with pumps in hybrid closed-loop systems, adjust insulin delivery in real-time based on interstitial glucose levels, achieving HbA1c reductions of 0.5-1.0% and reducing hypoglycemic events by up to 40%. Emerging technologies, such as fully closed-loop systems and implantable insulin reservoirs, promise further precision, approximating an “artificial pancreas.”

Despite these advancements, insulin therapy faces substantial challenges. Hypoglycemia, affecting 20-30% of insulin-treated patients annually, arises from mismatches between insulin doses and glucose availability, particularly during exercise, fasting, or medication errors. Severe hypoglycemia can cause seizures,





coma, or death, necessitating patient education on carbohydrate counting and glucagon use. Weight gain, reported in 50-70% of patients initiating insulin, stems from insulin's anabolic effects, reduced glycosuria, and compensatory hyperphagia to prevent hypoglycemia, complicating management in type 2 diabetes, where obesity is prevalent. Injection-related discomfort, needle phobia, and complex regimens deter adherence, with studies indicating that 20-30% of patients skip doses, increasing HbA1c by 0.3-0.8%. Socioeconomic barriers, including insulin costs (ranging from \$100-300/month in high-income countries) and supply chain disruptions in low-income regions, exacerbate disparities, with 50% of patients in sub-Saharan Africa lacking consistent access. Cultural stigma and inadequate diabetes education further hinder optimal therapy, particularly in rural settings.

Innovative research is addressing these challenges. Beta-cell regeneration, using induced pluripotent stem cells (iPSCs) or small-molecule agonists of beta-cell transcription factors (e.g., PDX1, MafA), aims to restore endogenous insulin production in type 1 diabetes. Encapsulation technologies protect transplanted beta cells from immune attack, with clinical trials reporting sustained insulin independence for up to 12 months. In type 2 diabetes, novel insulin-sensitizing agents, such as PPAR γ modulators and AMPK activators, enhance insulin signaling, reducing exogenous insulin requirements. Gene therapy, including CRISPR/Cas9-mediated correction of INS gene mutations or IRS-1 overexpression, offers potential for long-term metabolic correction. Pharmacogenomics is transforming insulin therapy by identifying genetic markers (e.g., KCNJ11 variants) that predict responsiveness to specific analogs, enabling personalized regimens. For example, patients with ABCC8 mutations may benefit from sulfonylureas over insulin, highlighting the value of genetic profiling.

Public health strategies are critical for addressing insulin resistance, the primary driver of type 2 diabetes. Obesity, affecting 650 million adults globally, increases visceral fat, which secretes adipokines (e.g., leptin, adiponectin) that impair insulin signaling. Sedentary behavior and high-glycemic diets exacerbate insulin resistance by elevating postprandial glucose and lipid levels. Structured lifestyle interventions, including 150 minutes/week of moderate aerobic exercise and low-carbohydrate diets, improve insulin sensitivity by 20-30%, reducing HbA1c by 0.5-1.0%. Community-based programs, such as diabetes prevention initiatives in Uzbekistan, integrate dietary counseling, physical activity promotion, and insulin access to curb disease progression. Digital health





tools, including mobile apps for glucose tracking and telemedicine platforms, enhance patient engagement, with studies reporting 15-20% improvements in adherence.

The economic and societal burden of diabetes, costing \$1.3 trillion annually, underscores insulin's pivotal role. By normalizing glycemia, insulin prevents microvascular complications, reducing retinopathy incidence by 60% and nephropathy progression by 50%. Macrovascular benefits, including 20-30% reductions in myocardial infarction risk, are achieved through intensive insulin therapy, particularly when initiated early. However, achieving these outcomes requires addressing systemic barriers. In Uzbekistan, where diabetes prevalence exceeds 7%, limited healthcare infrastructure and insulin affordability challenge care delivery. Multidisciplinary care models, involving endocrinologists, dietitians, and community health workers, are essential for patient empowerment. Policy interventions, such as insulin price caps and WHO's Global Diabetes Compact, aim to ensure universal access, targeting a 50% reduction in insulin-related mortality by 2030.

In conclusion, insulin's discovery heralded a new era in diabetes care, and its role remains unparalleled in managing hyperglycemia and preventing complications. From its intricate biosynthesis in beta cells to its sophisticated therapeutic applications, insulin embodies the synergy of molecular biology, pharmacology, and clinical innovation. Its ability to restore metabolic balance in type 1 diabetes and augment control in type 2 diabetes is transformative, yet challenges—hypoglycemia, weight gain, adherence, and access—persist. Next-generation analogs, smart delivery systems, and regenerative therapies are poised to enhance insulin's efficacy, while preventive strategies targeting insulin resistance through lifestyle modification are vital for curbing the diabetes epidemic. As global prevalence escalates, insulin's legacy as a therapeutic cornerstone endures, necessitating sustained scientific, clinical, and policy efforts to optimize its application, improve patient outcomes, and ensure equitable access. In Uzbekistan and beyond, insulin remains a beacon of hope, bridging the gap between scientific discovery and human health in the fight against diabetes.

References:

1. Karimov, A. A., & Saidova, F. M. (2020). Diabetes: Pathogenesis and Modern Approaches to Treatment. Tashkent: Medical Publishing House.
2. Murodov, B. Kh. (2018). The Role of Insulin Therapy in Endocrinology. Samarkand: Samarkand State Medical Institute.





3. Toshpulatova, N. R. (2022). Insulin Resistance and Its Molecular Basis in Diabetes. Tashkent: Uzbekistan Medical Journal.

