www.ijarp.com ISSN 2456-9992 Page: 01-10

International Journal Advanced Research Publications

Review Article

Volume: 02
Issue: 04

UNDERSTANDING ADVANCE INSULIN DEVELOPMENT: USING AI ADVANCEMENTS IN GLUCOSE RESPONSIVE FORMULATIONS (A COMPREHENSIVE REVIEW)

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Article Received: 02 March 2026, Article Revised: 20 March 2026, Published on: 10 April 2026

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DOI: https://doi-doi.org/101555/ijrpa.6380

ABSTRACT:

Glucose-responsive insulin systems or "smart insulins" represent a major breakthrough in diabetes care as these systems promise to manage diabetes automatically. Using AI technology, these systems are becoming more accurate and adaptable to real-time monitoring. This research aims to highlight advanced mechanisms of AI-based systems, the current issues, and the possible improvements in diabetes care.

Throughout much of the last century insulin served a central role in the advancement of peptide chemistry, pharmacology, cell signaling and structural biology. These discoveries have provided a steadily improved quantity and quality of life for those afflicted with

diabetes. The collective work serves as a foundation for the development of insulin analogs and mimetics capable of providing more tailored therapy. Advancements in patient care have been paced by breakthroughs in core technologies, such as semisynthesis, high performance chromatography, rDNA-biosynthesis and formulation sciences. How the structural and conformational dynamics of this endocrine hormone elicit its biological response remains a vigorous area of study. Numerous insulin analogs have served to coordinate structural biology and biochemical signaling to provide a first level understanding of insulin action.
The historical advancements in the synthesis of insulin analogs by multiple methods is reviewed with the specific structural elements of critical importance being highlighted. The functional refinement of this hormone as directed improved patient care with insulin analogs of more precise pharmacology is reported.

KEYWORDS: Autoimmunity; Gene polymorphism; Gene therapy; Genomic Risk Score; Insulin therapy; Pancreatic β cells; Personalized medicine; Personalized treatment; Stem cells; Type 1 diabetes.

INTRODUCTION:

Type 1 diabetes is an autoimmune condition that occurs as a result of destruction of the insulin producing β cells of the pancreatic islets, usually leading to severe endogenous insulin deficiency Without treatment, diabetic ketoacidosis will develop and eventually death will follow; thus, lifelong insulin therapy is needed for survival. Type 1 diabetes represents 5-10% of all diabetes, and diagnosis classically occurs in children but can also occur in adulthood. The burden of type 1 diabetes is expansive; it can result in long term complications, decreased life expectancy, and reduced quality of life and can add significant financial burden. Despite vast improvements in insulin, insulin delivery, and glucose monitoring technology, a large proportion of people with type 1 diabetes do not achieve glycemic goals. The massive burden of type 1 diabetes for patients and their families needs to be appreciated. The calculation and timing of prandial insulin dosing, often from food with unknown carbohydrate content, appropriate food and insulin dosing when exercising, and cost of therapy are all major challenges. The psychological realities of both acute management and the prospect of chronic complications add to the burden. Education programs and consistent surveillance for “diabetes burnout” are ideally available to everyone with type 1 diabetes.

PERSONALIZED DIAGNOSIS OF T1D

Although all patients with overt T1D exhibit pancreatic destruction and consequent dysregulation of blood glucose levels, not all cases of the disease are driven by the same factors or along the same timeline. Many patients experience a sometimes prolonged clinically silent phase in which it might have been possible to intervene and prevent or even reverse the course of disease. This knowledge has led to development of a staging classification system for T1D. Even once T1D is clinically evident, we are now beginning to appreciate that not all cases are the same, and that particular sub-types of the disease would benefit from distinct treatment strategies.

In this review, we discuss recent developments in the rapidly changing landscape of type 1 diabetes and highlight aspects of current epidemiology and advances in diagnosis, technology, and management. We do not cover the breadth of complications of diabetes or certain unique scenarios including psychosocial aspects of type 1 diabetes management, management aspects specific to older adults, and β cell replacement therapies. Our review is intended for the clinical reader, including general internists, family practitioners, and endocrinologists, but we acknowledge the critical role that people living with type 1 diabetes and their families play in the ongoing efforts to understand this lifelong condition.

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HYPERINSULININEMIA AND INSULIN RESISTANCE:

Experimental induction of insulin resistance in mice by disruption of insulin signaling in liver, skeletal muscle or adipose tissue causes hyperinsulinemia and can lead to diabetes10. Similarly, elegant studies on human subjects with monogenic mutations in insulin signaling components resulting in insulin resistance show similar high circulating insulin and consequent diabetes11. These data point towards the concept that both monogenic and

common forms of obesity also initially cause insulin resistance, which secondarily causes hyperinsulinemia, promoting fatty liver and hypertriglyceridemia.

Figure 1. Plausible pathways whereby insulin resistance is the initiating response to high fat diet feeding and obesity to cause hyperglycemia and hyperlipidemia.

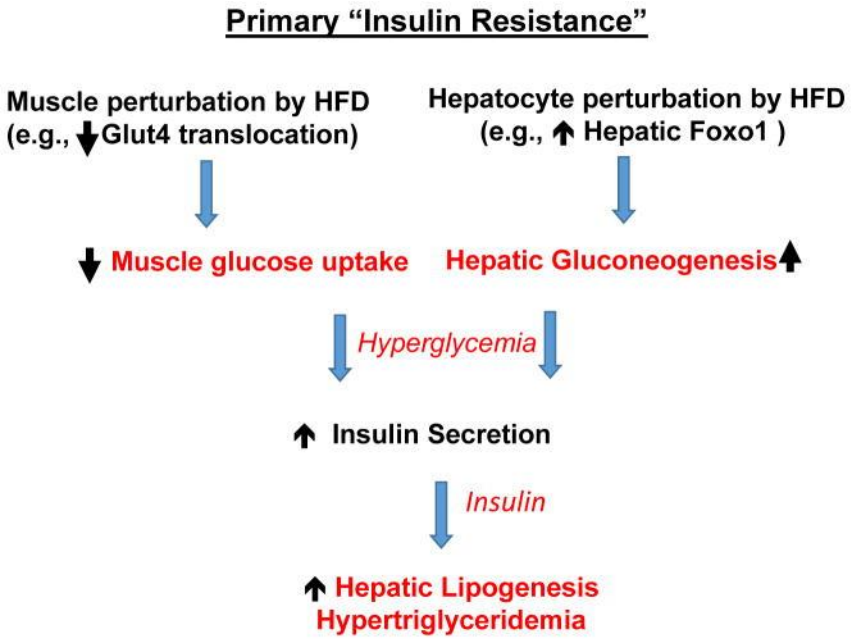

Fig 1.

UNDERSTANDING GLUCOSE _ RESPONSIVE INSULIN(GRI)

What is Glucose-Responsive Insulin?

Glucose-responsive insulin (GRI) is designed to release insulin in response to elevated blood glucose levels, mimicking how the human pancreas works naturally.

Unlike traditional insulin therapies that require external monitoring and manual administration, GRI acts autonomously, potentially reducing the need for frequent patient interventions.

Mechanisms of GRI

Enzyme-Based Systems:

Glucose Oxidase (GOx): One of the most common enzyme-based systems that catalyze the breakdown of glucose, triggering insulin release in response to glucose metabolism. GOx enzymes convert glucose into gluconic acid, lowering pH and triggering the insulin to be released from a hydrogel or polymer matrix.

Challenge: Hydrogen peroxide is a byproduct of this reaction, which can be toxic if not neutralized, so the system must be carefully controlled.

Polymer-Based Systems (e.g., Phenylboronic Acid):

Phenylboronic acid (PBA)-based polymers are another effective system. When glucose levels rise, glucose molecules bind to PBA, causing the polymer to swell and release insulin.

Benefit: This system is highly specific to glucose, reducing the risk of unintended insulin release when glucose is low.

pH-Responsive Hydrogels:

Some systems use hydrogels that respond to pH changes in the blood. When glucose is metabolized, it lowers the pH in the local environment, which

causes the hydrogel to expand and release insulin in a controlled manner.

Benefit: These systems can provide a more sustained release of insulin over time.

Nanoparticle Delivery Systems:

Nanoparticles have been explored as carriers for insulin. These nanoparticles can be designed to release insulin in response to glucose levels detected in the bloodstream or interstitial fluid.

Challenge: Ensuring consistent insulin release from nanoparticles and controlling their bio-distribution in the body is critical.

EPIDEMIOLOGY OF AGE-RELATED CHANGES IN GLUCOSE METABOLISM

According to the Third National Health and Nutrition Examination Survey (NHANES III) conducted from 1988 to 1994, the prevalence of type 2 diabetes in Americans 60–74 yr of age is >20% (22, 41). This percentage includes cases previously diagnosed by medical history and those newly diagnosed by fasting glucose or by oral glucose tolerance testing (OGTT). An additional 20% of this population meets criteria for impaired glucose tolerance (IGT), defined as a 2-h glucose level ≥140 mg/dl but <200 mg/dl by OGTT, and a fasting blood glucose not in the diabetic range (<126 mg/dl) (22). Prevalence data from 1976 to 1980 from NHANES II for diabetes and IGT in Americans 60–74 yr of age were similar (23); thus the high prevalence of glucose intolerance in the older population has persisted over the past two decades. Additional studies of older adults, including the Cardiovascular Health Study and Honolulu Heart Study, figure 2 show that the high prevalence of diabetes and IGT continues in people over age 75

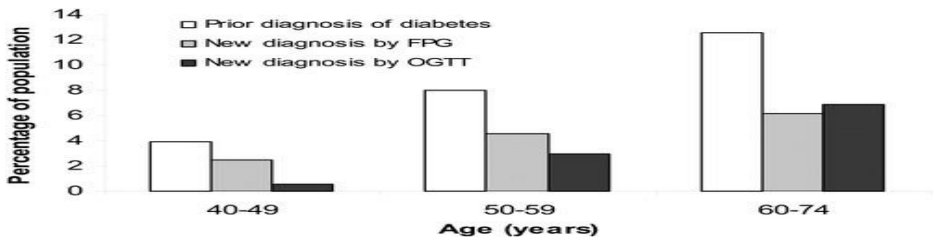

Fig 2.

ROLE OF INSULIN IN REGULATING INFLAMMATION:

According to Makhijani et al., disturbed insulin-dependent metabolic homeostasis leads to immune dysfunction, and sensitization to the action of this hormone may bring benefits in reducing inflammation . Systemic inflammation can lead to the development of many diseases, including cardiovascular diseases, cancer, non-alcoholic liver disease and diabetes. Due to the common nature of the problem, inflammatory diseases have been considered a more important cause of death worldwide . Hyperglycemia, an early complication of diabetes, can also indue inflammatory programming of macrophage. Hyperglycemia in type 2 diabetes (T2DM) may occur as a result of insulin resistance and inappropriate insulin secretion, and glycemic control can be achieved by administering insulin in an appropriate dose . It is believed that insulin may play an important immunomodulatory and anti-inflammatory role in the body

INSULIN: AN EVOLUTIONARILY CONSERVED MOLECULE:

Insulin signaling regulates blood glucose levels and is essential for maintaining energy storage, glucose metabolism, glycogenesis, lipogenesis, cellular growth, survival, and reproduction—additionally it plays a role in aging (Kenyon, 2010; Poretsky et al., 1999; Taguchi & White, 2008; Tatar et al., 2001). Physiologically, the cellular function of insulin is primarily mediated by IR, a member of the receptor tyrosine kinase family that is expressed on the cell surface as a heterodimer of two identical α2β2 subunits (reviewed by Lawrence, McKern, & Ward, 2007). IR regulates two major cell signaling cascades that affect either metabolic or mitogenic functions: (i) the phosphatidylinositol-3-kinase (PI3K)/AKT and (ii) RAS/ERK (extracellular-signal regulated kinase) signaling pathways (Figure 1) (described in detail by Belfiore, Frasca, Pandini, Sciacca, & Vigneri, 2009; Cantley, 2002; Liao & Hung, 2010; Roux & Blenis, 2004; Taniguchi, Emanuelli, & Kahn, 2006).

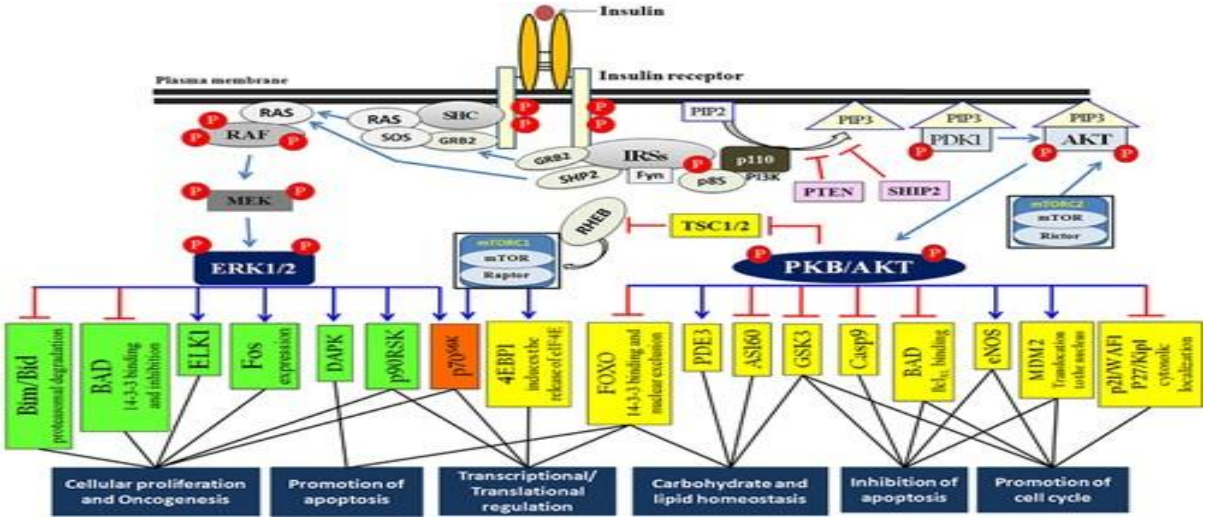

Fig 3.

BIOLOGICAL ACTION OF INSULIN:

The isolation and first clinical application of insulin just over 100 years ago provided the basis for life-saving treatments for people with Type 1 diabetes. Today millions of people with Type 1 diabetes and late-stage Type 2 diabetes are treated with insulin and insulin analogs that have been developed to achieve tight glycemic control. Some excellent reviews have recently been published to celebrate the centenary of the discovery of insulin and describe the development of insulin

FUTURE CHALLENGES FOR NEW ANTI DIABETIC DRUGS:

The advantage of biased agonists as therapeutic reagents would be that they could avoid on-target adverse effects arising from the activation of inappropriate signaling by specifically activating the signaling pathway that is required for disease treatment. Biased agonism of the insulin receptor by non-insulin ligands, which have metabolic effects but not mitogenic effects, has the potential to prevent the complications that may arise as a result of hyperinsulinemia or exogenous insulin.

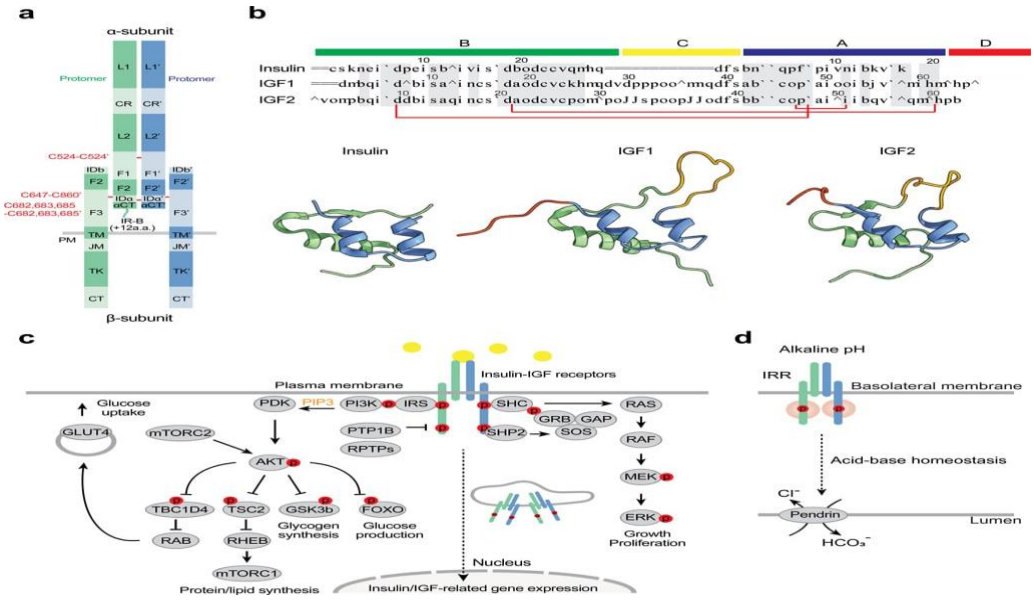

Figure 4 Structure and domain organization of insulin, IGFs, and IR family receptor.:

CONCLUSION:

Type 1 diabetes is a complex chronic condition with increasing worldwide prevalence affecting several million people. Several successes in management of type 1 diabetes have occurred over the years from the serendipitous discovery of insulin in 1921 to blood glucose monitoring, insulin pumps, transplantation, and immunomodulation. The past two decades have seen advancements in diagnosis, treatment, and technology including development of analog insulins, CGM, and advanced insulin delivery systems. Although we have gained a broad understanding on many important aspects of type 1 diabetes, gaps still exist. Pivotal research continues targeting immune targets to prevent or delay onset of type 1 diabetes. Although insulin is likely the oldest of existing modern drugs, no low priced generic supply of insulin exists anywhere in the world. Management of type 1 diabetes in under resourced areas continues to be a multifaceted problem with social, cultural, and political barriers

ABBREVIATIONS:

T2DM :Type 2 Diabetes Mellitus

IR :Insulin Resistance

IGF1R :Insulin-like Growth Factor 1 Receptor

MAPK :Mitogen-Activated Protein Kinase

PIK3CA :Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha

mTOR :Mammalian Target of Rapamycin

TNF :Tumor Necrosis Factor

IL6 :Interleukin-6

JAK2 :Janus Kinase 2

STAT3 :Signal Transducer and Activator of Transcription 3

VEGFA :Vascular Endothelial Growth Factor A

SHBG :Sex hormone-binding globulin

RAG :Recombination-activation genes

RAGE :Receptor for advanced glycation end-products

PTEN :Phosphatase and Tensin Homolog

GLUT4 :Glucose Transporter Type 4

AMPK :AMP-activated Protein Kinase

SGLT2 :Sodium-Glucose Cotransporter 2

GLP-1 :Glucagon-like Peptide-1

HbA1c :Glycated Hemoglobin

RCT :Randomized Controlled Trial

OS :Overall Survival

PFS :Progression-Free Survival

ROS :Reactive oxygen species

FFAs :Free fatty acids

TME :Tumor microenvironment

TAMs :Tumor-associated macrophages

Tregs :Regulatory T cells

MDSCs :Myeloid-derived suppressor cells

NCD :Non-communicable disease

LMIC :Low-and-middle income countries

WHO :World Health Organization

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