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Paradigm Shift in the Pathophysiology and Treatment of Insulin Resistance: From Epigenetic Determinants to the Continuous Glucose Monitoring (CGM) Revolution

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ABSTRACT

Introduction and purpose. The classical approach to metabolic diseases traditionally positioned insulin resistance as the primary cause of evolving pathology. However, modern evidence-based medicine indicates a critical need to redefine this view, demonstrating that hyperinsulinemia is an early, independent damaging factor that may precede clinical dysglycemia by a full decade. The fundamental aim of this study is to thoroughly analyze scientific evidence regarding the multifaceted pathogenesis, novel diagnostics, and modern treatment paradigms of insulin resistance and hyperinsulinemia.

A brief description of the state of knowledge. Based on a comprehensive review of 49 targeted publications, it was shown that insulin resistance pathophysiology involves complex DNA methylation mechanisms, aldosterone excess, and consequent changes in neural connectivity. Furthermore, genetic analyses definitively confirm the causal link between hyperinsulinemia and systemic complications like gout. A highly effective diagnostic tool is the widespread adoption of Continuous Glucose Monitoring (CGM) systems, which measure interstitial fluid glucose and enable rigorous analysis of Time in Range (TIR) and Time Above Range (TAR) in individuals without diagnosed diabetes. Therapeutically, pivotal recent trials demonstrate the high efficacy of multi-receptor incretin agonists (e.g., GLP-1, GIP, Glucagon) and SGLT2 inhibitors in radically improving insulin sensitivity and comprehensive cardiometabolic profiles.

Summary. Monitoring subclinical glucose fluctuations with advanced CGM technologies is a highly useful prophylactic tool. Interventions based on targeted lifestyle modifications and modern multi-target pharmacotherapy successfully promote the regression of prediabetes, significantly reducing the risk of vascular complications. Ensuring up-to-date classifications is necessary for accurate differential diagnosis and early implementation of targeted interventions.

Keywords: insulin resistance; hyperinsulinemia; continuous glucose monitoring; epigenetics; GLP-1 agonists; metabolic syndrome

Introduction and Paradigm Shift in Pathogenesis

Type 2 diabetes mellitus (T2DM) and its myriad of associated conditions represent a major clinical challenge to global healthcare systems and economic stability [1]. According to the latest 11th edition of the IDF Diabetes Atlas, published in 2025, the global prevalence of diabetes has reached 589 million adults [2]. Furthermore, current demographic estimates suggest that this number will substantially increase to nearly 853 million by 2050 [3]. A critical public health concern remains that an estimated 252 million adults are living with diabetes completely undiagnosed, highlighting a significant gap in early detection protocols [4].

In the face of these escalating projections, thoroughly understanding the metabolic mechanisms foreshadowing the disease remains a paramount scientific priority [5]. In the classical academic medical approach to pathophysiology, it was traditionally assumed that progressive peripheral tissue resistance to insulin's biological action was the singular primary phenomenon [6]. According to this traditional model, receptor blockade at the tissue level forces pancreatic beta cells to increase hormone production proportionally, ultimately leading to compensatory hyperinsulinemia [7]. However, advanced conceptual analyses published in leading journals indicate that treating hyperinsulinemia solely as a secondary symptom may be a dangerous oversimplification [8]. It is crucial for medical specialists to understand these basics of insulin resistance to implement effective clinical strategies [9].

The dynamic relationship between insulin resistance and hyperinsulinemia is strictly bidirectional [10]. It is now heavily suggested that primary insulin hypersecretion, often induced by an environmental energy oversupply, can down-regulate its own cellular receptors, thereby directly initiating tissue resistance [7]. This paradigm shift has important diagnostic and preventive implications [11]. Robust population studies have documented that an elevated baseline fasting insulin concentration is an extremely early predictor of subsequent weight gain and metabolic decline [12]. Pronounced hyperinsulinemia has been found to chronically precede measurable elevations in blood glucose levels, often by a decade or more [13]. Therefore, modern clinical guidelines classify hyperinsulinemia as an early, independent marker of developing metabolic dysfunction rather than a mere byproduct [14]. This pivot directs clinical practice to actively look for insulin abnormalities in normoglycemic patients to institute early prevention [15].

Moreover, recent comprehensive analyses of the NHANES program demonstrated that the prevalence of insulin resistance among young American adults (18-44 years) without diabetes is considerably high, hovering around 40-44% [16]. This young resistant population also

exhibits significantly elevated rates of concurrent hypertension and hypercholesterolemia, proving that insulin resistance is a systemic threat long before clinical diabetes manifests [17]. Furthermore, precise anthropometric measurements and blood-based biomarkers are vital for assessing visceral adipose tissue, which strongly correlates with the severity of systemic insulin resistance [18]. Obesity and T2DM share profound connections in epidemiology and pathogenesis, necessitating combined treatment approaches [5].

Review Methods

The literature review was based on the analysis of 49 peer-reviewed scientific publications [19]. Extensive databases, including PubMed, PubMed Central, and Google Scholar, were systematically searched for articles published and updated between 2018 and 2026 [20, 21], rigorous search process utilized specific English keywords: "insulin resistance", "hyperinsulinemia", "continuous glucose monitoring", "epigenetics", "GLP-1 receptor agonists", "SGLT2 inhibitors", and "metabolic syndrome" [4]. The final synthesis included primary research articles, meta-analyses, bidirectional Mendelian randomization studies, and the latest clinical guidelines from international scientific societies (e.g., ADA, IDF) [2, 20, 21]. The resulting paper is structured as a comprehensive narrative review [19].

Etiopathogenesis

From Epigenetics through Aldosterone to the Central Nervous System

The underlying mechanisms of insulin resistance are complex and involve at the genetic, epigenetic, and neurohormonal levels. Hereditary predisposition to insulin axis signaling disorders is determined, among other factors, by multiple single-nucleotide polymorphisms (SNPs [22]. However, the modern environment also exerts a significant impact on gene expression through acquired epigenetic modifications, such as DNA methylation or histone modifications. These intricate processes, rapidly activated by poor diet and sedentary behavior, downregulate the expression of genes promoting insulin sensitivity [23]. Crucially, these modifications occur without altering the underlying nucleotide sequence.

Furthermore, longitudinal studies indicate a powerful intergenerational transmission of insulin resistance. It is proven that maternal obesity or gestational diabetes (GDM) can induce lasting epigenetic modifications in the developing fetus, exponentially increasing the risk of early obesity in the offspring [24]. Epigenetic profiling is also rapidly finding novel diagnostic

applications [25]. Sophisticated biomarkers based on large-scale DNA methylation, such as the Methylation Risk Score (MRS), have been developed to transform risk stratification [26]. A recent 2025 study validated an MRS using 87 specific methylation sites that can predict future macrovascular events with an Area Under the Curve (AUC) of 0.81-0.84, showing higher predictive value than traditional clinical risk scores such as SCORE2-Diabetes and Framingham. Additionally, a similar epigenetic profiling encompassing 37 specific methylation sites provides a highly accurate prediction of chronic kidney disease (CKD) development in newly diagnosed patients, achieving an AUC of 0.87 and a remarkable negative predictive value of 94.6% [25].

Beyond genetics, the renin-angiotensin-aldosterone (RAA) system also modulates tissue sensitivity. Increased systemic aldosterone concentrations promote tissue fibrosis and exacerbate chronic oxidative stress. This pathophysiological cascade profoundly impairs insulin signaling in skeletal muscle by overactivating mineralocorticoid receptors (MR). Consequently, excess aldosterone is recognized as an independent, potent factor promoting the rapid development of metabolic syndrome [27].

Anatomically, strong correlations with insulin resistance are increasingly evident in the structural integrity of the central nervous system. Obesity, coupled with insulin resistance, is associated with altered brain connectivity, particularly in the prefrontal cortex and critical reward centers [28]. However, the implementation of strict low-calorie interventions demonstrates a remarkable capacity to induce structural restorative changes in advanced magnetic resonance imaging, indicating that vital neuroplasticity is preserved despite metabolic insults [29].

Systemic Consequences, Microangiopathies, and Hyperuricemia

Chronic hyperinsulinemia in resistant individuals profoundly impairs the function of multiple organ systems [16]. Macrovascular complications are intrinsically associated with early endothelial dysfunction and progressive arterial stiffness [30]. Extensive analyses have shown the presence of elevated cardiometabolic risk profiles in patients with insulin resistance extremely early in adulthood, totally without overt diabetes [15].

Regarding the frequent coexistence of gout with metabolic disorders, bidirectional Mendelian randomization analyses have definitively confirmed a true causal relationship. It is now proven that genetically determined hyperinsulinemia directly reduces the renal excretion of uric acid, leading secondarily to systemic hyperuricemia and subsequent joint crystal deposition [31].

These detrimental phenomena multiply rapidly in the complex coexistence of multiple pathomechanisms [32]. A prime example of this is a rapidly emerging diagnostic category described as "double diabetes" [33]. This term refers to patients with classic autoimmune type 1 diabetes who, as a result of weight gain and lifestyle factors, additionally develop severe tissue resistance traditionally attributed to T2DM [34]. This overlap significantly complicatesglycemic control and massively accelerates vascular complications.

The blurring of boundaries between classic, binary diabetes types creates profound diagnostic challenges for modern clinicians. To accurately differentiate double diabetes from other metabolic subphenotypes and to implement appropriate treatment, the immediate use of advanced biomarkers is essential. This includes rigorous, continuous assessment of C-peptide levels. A broad panel of autoantibody testing (including GADA, IA-2, and ZnT8) alongside precise measurements of tissue resistance markers is strictly required to confirm this dual pathology [33].

Furthermore, untreated insulin resistance directly correlates with progressive microdamage to peripheral nerves [16]. It is also associated with a significantly increased risk of developing mild cognitive impairment (MCI) and neurodegeneration [35]. From a hopeful clinical perspective, the extended observation phase of the DPPOS trial definitively demonstrated that successful regression from prediabetes to normal glucose tolerance is associated with a drastically reduced risk of developing future microvascular complications [26].

Application of Continuous Glucose Monitoring (CGM) Systems

Traditionally, the clinical evaluation of glucose absorption heavily relied on static morning fasting glucose measurements and glycated hemoglobin (HbA1c) testing [36]. Unfortunately, these isolated values create a highly averaged profile, potentially masking dangerous postprandial glycemic peaks and silent nocturnal hypoglycemic events [6]. Continuous glucose monitoring (CGM) systems currently serve as an increasingly utilized method for this vital evaluation [37]. It should be noted that these modern systems measure glucose concentration in interstitial fluid rather than directly in capillary blood. This technological distinction entails a natural physiological lag time during periods of extremely rapid glycemic fluctuations [38].

The American Diabetes Association (ADA) currently incorporates CGM technologies into the proactive monitoring of high-risk individuals [21]. Novel studies in populations completely free of diabetes demonstrate the immense utility of CGM in highlighting early, subclinical deviations from the metabolic norm [39]. Glycemic variability (GV) accurately assessed with these systems has been independently linked to severe cardiovascular risk markers [32]. Measurements such as "Time in Range" (TIR) and "Time Above Range" (TAR) provide critical

prognostic data [40]. Recent extensive community-based cohort studies have defined that healthy adults maintain their glucose levels in the strict physiological TIR (70-140 mg/dL) for an average of 87% of the day [41]. Moreover, the applicability of these monitoring metrics extends across all demographics, providing vital insights even in very old adults with and without established diabetes [42]. These key metrics and their definitions are clearly summarized in Table 1 [21].

Table 1. Continuous Glucose Monitoring (CGM) metrics and their clinical significance.

Caption: An overview of CGM metrics (TIR, TAR, GV), their definitions based on clinical guidelines, and their application in identifying disorders in patients without diagnosed diabetes [21]. Glucose concentrations are expressed in mg/dL (1 mg/dL = 0.0555 mmol/L) [40].

CGM Metric	Clinical definition	Significance in pathophysiological assessment
Time in Range (TIR)	Percentage of time spent in the 70-140 mg/dL range (physiological norm) [41].	In healthy adults, it averages around 87%. A decrease in TIR suggests early dysglycemia [41].
Time Above Range (TAR)	Percentage of time with glucose concentrations > 140 mg/dL [40].	A metric correlating with an increased risk of developing T2DM [40].
Glycemic Variability (GV)	Amplitude of glucose curve fluctuations [32].	Independent cardiovascular risk marker [32].

The advanced integration of CGM data with artificial intelligence (AI) algorithms powerfully supports the precise identification of differences in glucose metabolism [34]. Studies strongly indicate that machine learning methods can accurately differentiate isolated muscle insulin resistance from a primary pancreatic beta-cell secretory defect solely on the basis of postprandial glycemic fluctuations [4]. Sophisticated machine learning models trained on glucose time series from oral glucose tolerance tests (OGTTs) can predict these subphenotypes with high accuracy. As recently demonstrated in 2025, the predictive area under the curve (AUC) reaches 95%. For primary pancreatic beta-cell defects, the AUC is highly reliable at 89%. These metrics are visualized in Table 2 [34].

Table 2. Classification of metabolic subphenotypes via AI and CGM.

Caption: Predictive accuracy of machine learning models in identifying insulin resistance subphenotypes based on continuous glucose monitoring data [34].

Identified Subphenotype	AI Detection Accuracy (AUC)	Clinical Implications
Muscle Insulin Resistance	95% [34].	Indicates a need for targeted skeletal muscle sensitization and specific resistance training [34].
Beta-Cell Dysfunction	89% [34].	Suggests early secretory exhaustion, requiring prompt beta-cell protective therapies [34].

However, it must be noted that the broad application of AI in medicine still faces limitations related to the sheer heterogeneity of wearable device data and potential algorithmic bias. This necessitates rigorous validation across highly diverse population groups before universal clinical rollout [34]. Based on continuous CGM results, interactive Digital Therapeutics (DTx) are also being rapidly developed. These digital modules offer real-time behavioral interventions that have been directly linked in modern meta-analyses to a significant mean reduction in HbA1c of approximately 0.54% in individuals with early dysglycemia [43]. The everyday use of glycemic monitoring is also vastly expanding into cutting-edge sports medicine applications [39].

Directions for Pharmacological Interventions

In the comprehensive treatment of metabolic disorders, the absolute foundation remains sustainable body weight reduction achieved through strict dietary modifications [36]. In patients battling high-degree obesity, exceptionally high efficacy is consistently noted following bariatric surgery (e.g., sleeve gastrectomy). Such surgical interventions contribute to radically improved tissue resistance and a rapid reduction in metabolic dysfunction-associated steatotic liver disease (MASLD) [3].

Incretin-based therapies, including DPP-4 inhibitors, have established a foundational role in maintaining glucose homeostasis by prolonging the half-life of endogenous GLP-1 [44]. Simultaneously, significant progress has been made in pharmacological science, firmly

underpinned by novel multi-target drug strategies [45]. Glucagon-like peptide-1 (GLP-1) receptor agonists uniquely facilitate substantial weight loss by suppressing hypothalamic appetite signals and significantly delaying gastric emptying [45]. In the landmark SELECT trial, it was conclusively observed that 69.5% of participants with overweight and preexisting cardiovascular disease treated with semaglutide achieved complete return to normoglycemia after 156 weeks of therapy, compared with 35.8% in the placebo group [46]. Furthermore, this trial demonstrated that body weight loss plateaued around 65 weeks. Yet, the drug continued to yield profound cardioprotective effects and marked reductions in inflammatory markers (hsCRP) independently of the weight lost [46].

Even more advances are currently observed in the latest research on novel polyreceptor molecules [41]. While dual agonists like tirzepatide paved the way, the newest phase 3 clinical trial data from the 2026 TRANSCEND-T2D-1 study highlighted the high clinical efficacy of retatrutide, a triple GIP/GLP-1/glucagon receptor agonist. In this massive trial, obese patients with type 2 diabetes treated with retatrutide achieved a substantial weight reduction of 16.8% (an average of 36.6 lbs) over just 40 weeks, alongside a clinically relevant 2.0 percentage point drop in HbA1c levels. Unlike earlier generations of drugs, patients on retatrutide did not experience a weight loss plateau at 40 weeks, demonstrating its high efficacy in reversing deep-seated metabolic syndrome [47].

Simultaneously, SGLT2 inhibitors (gliflozins) operate on an entirely different but equally vital axis. They directly induce therapeutic glycosuria by chemically lowering the renal threshold for glucose reabsorption in the proximal tubules. They exhibit extensively documented nephro- and cardioprotective features, notably by promoting profound natriuresis, which favorably activates tubuloglomerular feedback and immediately reduces destructive intraglomerular pressure. Furthermore, on a deeply molecular level, these molecules stimulate a mild metabolic shift towards fatty acid oxidation. Crucially, SGLT2 inhibitors create a state of cellular "hypoxia mimicry". This metabolic deprivation strongly stimulates sirtuin-1 (SIRT1), which, in turn, stabilizes and activates hypoxia-inducible factor 2-alpha (HIF-2α). The stabilization of HIF-2α directly cascades into a massive increase in hepatic and renal erythropoietin (EPO) production, effectively suppressing hepcidin and improving vital oxygen delivery to the failing heart and fibrotic kidneys [48]. This pleiotropic profile is especially beneficial for patients suffering from heart failure with coexisting chronic kidney disease, where SGLT2 inhibitors significantly improve clinical outcomes [49, 50]. The defining characteristics of these revolutionary medications are detailed in Table 3 [45].

Table 3. Modern drug classes in pharmacotherapy targeting the pathomechanisms of insulin resistance.

Caption: An overview of innovative drug classes (GLP-1 agonists, multi-receptor agonists, and SGLT2 inhibitors) detailing their mechanisms of action and clinically proven effects in metabolism control [45].

Drug class	Primary mechanism of action	Confirmed metabolic and clinical effects
GLP-1 Agonists (e.g., semaglutide)	Activation of incretin receptors and delayed gastric emptying [45].	Normoglycemia in 69.5% of participants in the SELECT trial [46].
Triple Agonists (e.g., retatrutide)	Synergistic, combined activation of GIP, GLP-1 and glucagon receptors [47].	16.8% weight loss and 2.0% A1C reduction at 40 weeks (TRANSCEND-T2D-1 trial) [47].
SGLT2 Inhibitors (gliflozins)	Induction of glycosuria and activation of the HIF-2α / EPO pathway [48].	Kidney protection, increased hematocrit, and improved cardiac ejection fraction [48].

Limitations of the review

Certain inherent limitations of this specific study should be transparently noted [19]. Given the methodological nature of a narrative review, the initial selection of sources may have been inadvertently subject to unintended selection bias [19]. Moreover, the highly advanced technologies discussed, particularly machine learning algorithms in CGM analysis, represent incredibly dynamic and fast-moving scientific fields [8]. While the current AI predictive models and the phase 3 efficacy results of triple agonists are groundbreaking, they require continued tracking and lifelong validation in real-world, large-scale clinical registries [47].

Conclusions

Metabolic disorders, heavily encompassing both insulin resistance and subclinical hyperinsulinemia, essentially result from the intricate, lifelong interaction of genetic,

epigenetic, and environmental factors. The widespread utilization of continuous glucose monitoring (CGM) technologies creates valuable opportunities to analyze subtle glucose fluctuations in at-risk individuals, vastly expanding the true scope of early prophylaxis. In the modern realm of clinical interventions, novel medications from the GLP-1 and GIP agonist groups, as well as SGLT2 inhibitors, effectively facilitate multidirectional, deep-tissue improvements in metabolic parameters [41]. The early and highly targeted identification of patients at risk of progressing to T2DM, combined with smart lifestyle modifications and the most potent available pharmacological methods, remains an absolute priority in contemporary, evidence-based healthcare.

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Disclosure Section

Declaration of generative AI and AI-assisted technologies in the writing process

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