AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 6. No 04. Aprel ,2026

INSULIN RESISTANCE AND β-CELL FAILURE IN DIABETES MELLITUS

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Abstract

Diabetes mellitus is a complex, multifactorial metabolic disease in which insulin resistance and functional impairment of β-cells act as interrelated processes in its pathogenesis. Insulin resistance leads to decreased glucose utilization in peripheral tissues, to which β-cells initially respond with compensatory hypersecretion. However, over time, their structural and functional reserves become exhausted. As a result, chronic hyperglycemia, along with pathobiochemical mechanisms such as lipotoxicity and glucotoxicity, further aggravates β-cell dysfunction. An integrative analysis of these two key components is essential for understanding the progression of diabetes and serves as a theoretical basis for developing individualized therapeutic strategies.

Keywords

insulin resistance, β-cell dysfunction, hyperglycemia, compensatory hypersecretion, glucotoxicity, lipotoxicity, glucose homeostasis, pathogenesis of diabetes.

Diabetes mellitus is considered one of the most urgent global public health problems of the 21st century. The disease is spreading rapidly, reducing the quality of life of millions of people and placing a significant clinical and economic burden on healthcare systems. In particular, patients with type 2 diabetes frequently develop cardiovascular, renal, nervous, and ocular complications. Moreover, chronic hyperglycemia negatively affects not only physical but also psychological health (4). Due to the insufficient manifestation of symptoms in the early stages of the disease, diagnosis is often delayed, which increases the risk of complications and limits the effectiveness of treatment options. Therefore, in-depth study of the pathogenesis and development mechanisms of diabetes mellitus is one of the most urgent scientific and clinical tasks today (13). The main pathogenetic mechanisms of diabetes mellitus are insulin resistance and β-cell dysfunction, which act as mutually reinforcing processes. Insulin resistance reduces glucose uptake in peripheral tissues, leading to compensatory hypersecretory activity of β-cells (6). However, as a result of long-term metabolic stress, glucotoxicity, and lipotoxicity, β-cells lose their functional and structural reserve capacity, chronic hyperglycemia develops, and the disease progresses to decompensation. Therefore, the integrative analysis of insulin resistance and β-cell dysfunction is of great importance for early diagnosis, individual prognosis, and the development of effective treatment strategies for diabetes mellitus (11).

In addition, epidemiological trends in the spread of diabetes mellitus further increase its relevance. Currently, the disease is rapidly increasing not only in high-income countries but also in developing countries. As a result, early detection and effective management of the disease are becoming important social and economic issues. The clinical course of the disease is often

AMERICAN ACADEMIC PUBLISHER
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ISSN NUMBER: 2692 - 5206 Volume 6. No 04. Aprel ,2026

asymptomatic for many years, and the hidden development of metabolic disorders complicates the efficient allocation of healthcare resources. Therefore, a deep understanding and integrative analysis of pathogenetic mechanisms are necessary (18). The interrelationship between insulin resistance and β-cell dysfunction is considered a central mechanism of diabetes mellitus (15). Reduced insulin action in peripheral tissues forces β-cells into overactivity, initiating compensatory hypersecretion. However, long-term metabolic stress, glucotoxicity, and lipotoxicity reduce the structural and functional reserve of β-cells (7). As a result, chronic hyperglycemia develops, and complications progress more rapidly. The integrative analysis of these processes helps not only to understand disease mechanisms but also to develop individualized therapy approaches and effective preventive strategies (10).

Over the past decades, concepts of diabetes pathogenesis have significantly evolved. The initial model, known as the "triumvirate," explained the disease through insulin resistance, β-cell dysfunction, and increased hepatic glucose production (2). Later, this concept was expanded into the "ominous octet" model proposed by DeFronzo and colleagues, which includes eight key mechanisms: impaired insulin action in peripheral tissues, β-cell failure, hepatic and adipocyte metabolism disorders, impaired intestinal glucose absorption, increased renal glucose reabsorption, central nervous system effects, and hepatokine mechanisms (3).

Studies by various scientists show a contradiction between insulin resistance and β-cell dysfunction. For example, Kahn et al. emphasized that impaired insulin signaling in peripheral tissues is the primary catalyst of type 2 diabetes, while Prentki and Nolan demonstrated the crucial role of compensatory β-cell hypersecretion in maintaining glucose homeostasis in early stages. Meanwhile, Ashcroft and Rorsman highlighted the complexity of β-cell electrical activity and insulin secretion mechanisms, as well as their rapid exhaustion due to glucotoxicity and lipotoxicity (4). These contradictions indicate that treatment of diabetes mellitus requires not only improvement of insulin sensitivity or β-cell support but also an integrative approach targeting multiple mechanisms simultaneously (12).

The central pathogenesis of diabetes mellitus is based on insulin resistance and β-cell dysfunction. Impaired insulin signaling in peripheral tissues such as muscle, adipose tissue, and liver reduces glucose uptake, resulting in hyperglycemia. Excess lipids and cytokines inhibit insulin receptor and post-receptor signaling pathways, further decreasing glucose utilization. Increased glucose load leads to compensatory hypersecretion of insulin by β-cells. However, prolonged overload disrupts their electrical activity and insulin secretion, causing structural damage and β-cell failure (15). Insulin resistance and β-cell dysfunction form a mutually reinforcing cycle in the development of diabetes mellitus (17). Reduced peripheral glucose utilization stimulates compensatory β-cell activity, while long-term metabolic stress leads to β-cell exhaustion and chronic hyperglycemia. Chronic hyperglycemia (glucotoxicity) and elevated free fatty acids (lipotoxicity) exert toxic effects on β-cells, further reducing insulin secretion and worsening metabolic disturbances. Thus, insulin resistance and β-cell dysfunction create a self-reinforcing cycle, leading to persistent hyperglycemia and disease decompensation. Consequently, clinical complications develop, necessitating an integrative therapeutic approach (19).

Furthermore, the interrelationship between insulin resistance and β-cell dysfunction plays a central role in disease progression. Reduced glucose utilization in peripheral tissues forces β-

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cells into overactivity, resulting in compensatory hypersecretion. However, prolonged metabolic stress, glucotoxicity, and lipotoxicity reduce β-cell functional and structural reserve (12). As a result, chronic hyperglycemia develops, insulin resistance worsens, and this cyclical process becomes the central mechanism of diabetes pathogenesis. Understanding these integrative mechanisms is essential for early clinical diagnosis, selection of individualized therapy, and reduction of complications. In addition, therapeutic strategies aimed at preventing or reducing glucotoxicity and lipotoxicity can slow disease progression and prevent decompensation (5).

This analysis clearly demonstrates the interrelationship between insulin resistance and β-cell dysfunction in the pathogenesis of diabetes mellitus. The results confirm that impaired insulin action in peripheral tissues plays a dominant role in the early stages of the disease, while long-term metabolic stress and glucotoxicity reduce β-cell compensatory capacity, leading to disease decompensation (20). From a clinical perspective, this integrative analysis is highly important. Early detection of insulin resistance allows the development of individualized approaches aimed at maintaining glucose stability and protecting β-cells (7). In addition, strategies targeting β-cell function and reducing glucotoxicity and lipotoxicity can slow disease progression and reduce complication risk. Thus, integrative analysis of pathogenetic mechanisms enables both a deeper understanding of the disease and the development of effective diagnostic and therapeutic approaches (16).

The pathogenesis of diabetes mellitus is based on a cyclic interaction between peripheral insulin resistance and β-cell dysfunction. Impaired insulin action in peripheral tissues acts as the primary catalyst of the disease, while compensatory β-cell hypersecretion is eventually exhausted due to long-term metabolic stress, leading to chronic hyperglycemia. Glucotoxicity and lipotoxicity accelerate disease progression and reduce β-cell functional reserve. Therefore, integrative analysis of insulin resistance and β-cell dysfunction provides a scientific basis for early diagnosis and individualized therapeutic strategies in diabetes mellitus.

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