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"THE ROLE OF OBESITY-RELATED INSULIN RESISTANCE IN MOLECULAR MECHANISMS AND THE DEVELOPMENT OF TYPE 2 DIABETES MELLITUS"

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Abstract

Insulin resistance is a complex metabolic disorder characterized by a decreased sensitivity of peripheral tissues—particularly skeletal muscle, liver, and adipose tissue—to insulin action. It is considered a central pathogenic mechanism in the development of type 2 diabetes mellitus (T2DM). Recent scientific studies indicate that insulin resistance is not merely a disorder of carbohydrate metabolism but a key component of the broader metabolic syndrome.

Obesity, especially the accumulation of visceral adipose tissue, is one of the most important predisposing factors for the development of insulin resistance. Adipose tissue is now recognized as an active endocrine organ that secretes various biologically active substances, including adipokines (leptin, adiponectin, resistin) and pro-inflammatory cytokines (TNF-α, IL-6, CRP). The increased production of these mediators leads to a state of chronic low-grade inflammation, which disrupts normal insulin signaling pathways.

At the molecular level, insulin resistance is associated with impairment of key signaling pathways such as IRS-1 (insulin receptor substrate-1), PI3K/Akt, and MAPK, resulting in reduced translocation of GLUT4 transporters to the cell membrane. Consequently, glucose uptake by muscle and adipose cells is impaired, leading to elevated blood glucose levels. This process is initially compensated by hyperinsulinemia; however, over time, it causes functional stress and eventual decompensation of pancreatic β-cells.

The clinical consequences of insulin resistance are not limited to type 2 diabetes mellitus. It also significantly increases the risk of arterial hypertension, dyslipidemia, atherosclerosis, and cardiovascular diseases. Therefore, early detection of insulin resistance and implementation of preventive strategies are considered important tasks of modern endocrinology.

This review article systematically analyzes the pathophysiological mechanisms of obesity-related insulin resistance, its molecular basis, its relationship with metabolic syndrome, and the stages of progression toward type 2 diabetes mellitus based on current scientific literature. In addition, it discusses disruptions in insulin signaling pathways, the role of inflammatory mediators, and modern concepts such as mitochondrial dysfunction. The article also reviews current approaches for early diagnosis and therapeutic strategies aimed at slowing the progression of insulin resistance.

Keywords

insulin resistance, obesity, type 2 diabetes mellitus, metabolic syndrome, adipokines, inflammation, PI3K/Akt signaling pathway, GLUT4, hyperglycemia.

Introduction

Diabetes mellitus is currently considered one of the most significant chronic metabolic diseases facing the global healthcare system. According to the World Health Organization (WHO) and the International Diabetes Federation (IDF), the incidence of diabetes has been

increasing sharply over recent decades, and type 2 diabetes mellitus (T2DM) constitutes the majority of cases. One of the most important pathogenetic mechanisms underlying this disease is insulin resistance, which leads from obesity to the development of complex metabolic disturbances.

Obesity, particularly the accumulation of visceral adipose tissue, is a widespread problem in modern society. It is not only a disturbance of energy balance but also an endocrine-active tissue that profoundly alters the organism's metabolism. Adipose tissue secretes various biologically active molecules, including adipokines and pro-inflammatory cytokines, which directly affect insulin signaling pathways and reduce peripheral tissue sensitivity to insulin.

As a result of the development of insulin resistance, glucose utilization is impaired, hepatic glucose production increases, and blood glucose levels remain persistently elevated. This condition is initially accompanied by compensatory hyperinsulinemia; however, over time it leads to functional exhaustion of pancreatic β-cells and a reduction in their secretory capacity. Consequently, through the prediabetic stage, type 2 diabetes mellitus develops.

At the molecular level, insulin resistance is considered a complex process associated with disturbances in signaling pathways such as IRS-1, PI3K/Akt, and MAPK, impaired translocation of GLUT4 transporters to the cell membrane, as well as oxidative stress and mitochondrial dysfunction. Therefore, insulin resistance should not be viewed only as a disorder of glucose metabolism but also as a central component of the metabolic syndrome.

From this perspective, the aim of this review article is to analyze the obesity-related mechanisms of insulin resistance, its molecular basis, its relationship with metabolic syndrome, and the stages of progression toward type 2 diabetes mellitus based on modern scientific literature.

1. Mechanism of Obesity-Related Insulin Resistance Initiation

Obesity, particularly the accumulation of visceral adipose tissue, is considered one of the most important initiating factors of insulin resistance. Adipose tissue is not only an energy storage organ but also an endocrine-active organ that produces adipokines such as leptin, adiponectin, resistin, as well as pro-inflammatory cytokines such as TNF-α and IL-6.

In conditions of obesity, the balance of these biologically active substances is disrupted, leading to a state of chronic low-grade inflammation. Increased levels of free fatty acids in the blood lead to lipid accumulation in liver and muscle cells, which creates a basis for the disruption of insulin signaling. As a result, processes from the level of insulin receptors to intracellular signaling pathways become impaired.

2. Molecular Level Disturbances

The main pathogenesis of insulin resistance is based on the disruption of insulin signaling pathways. Under normal conditions, when insulin binds to its receptor, insulin receptor substrate-1 (IRS-1) is activated, and through the PI3K/Akt signaling pathway, translocation of GLUT4 transporters to the cell membrane is ensured.

However, in insulin resistance:

Phosphorylation of IRS-1 is impaired

Activity of the PI3K/Akt pathway is reduced

Translocation of GLUT4 is decreased

As a result, glucose cannot adequately enter muscle and adipose cells, and hyperglycemia develops. In addition, activation of the MAPK pathway enhances proliferative and inflammatory processes, further worsening insulin signaling impairment.

3. Role of Inflammation and Oxidative Stress

Recent scientific studies indicate that inflammatory processes play an important role in the development of insulin resistance. Activation of macrophages in adipose tissue leads to increased production of cytokines such as TNF-α and IL-6.

These cytokines:

inhibit insulin signaling pathways

activate serine kinases

block insulin receptor substrates

At the same time, mitochondrial dysfunction and increased production of reactive oxygen species (ROS) intensify oxidative stress, further deepening cellular damage.

4. Clinical Consequences and Progression to Type 2 Diabetes

Insulin resistance is initially accompanied by compensatory hyperinsulinemia, meaning that pancreatic β-cells increase insulin secretion. However, over time, β-cells become exhausted and their secretory function decreases.

As a result, the following stages develop:

insulin resistance

prediabetes (impaired glucose tolerance)

type 2 diabetes mellitus

During this process, additional metabolic disorders such as lipid metabolism disturbances, arterial hypertension, and atherosclerosis also occur.

5. Relationship with Metabolic Syndrome

Insulin resistance is considered the central component of metabolic syndrome. It is associated with obesity, dyslipidemia, hypertension, and hyperglycemia. This syndrome significantly increases the risk of cardiovascular diseases and is regarded as a major global health problem.

CONCLUSION

Insulin resistance is a central pathophysiological mechanism in the progression from obesity to type 2 diabetes mellitus. Modern scientific data interpret this condition not only as a disorder of glucose metabolism but also as a complex metabolic dysfunction involving adipokines, inflammatory mediators, and oxidative stress.

Obesity, particularly the accumulation of visceral adipose tissue, leads to disruption of insulin signaling pathways (IRS-1, PI3K/Akt, MAPK), resulting in decreased GLUT4 transporter activity and reduced glucose uptake into cells. Although this process is initially compensated by hyperinsulinemia, it eventually leads to pancreatic β-cell dysfunction and the development of type 2 diabetes mellitus.

Therefore, early detection of insulin resistance and slowing its progression is of great clinical importance in preventing metabolic syndrome, cardiovascular diseases, and diabetic complications. Modern approaches include lifestyle modification, increased physical activity, and pharmacological therapy.

Overall, a deep understanding of insulin resistance provides a scientific basis for understanding the pathogenesis of type 2 diabetes mellitus and for developing effective preventive and therapeutic strategies.

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