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INSULIN RESISTANCE: MECHANISMS, CLINICAL IMPLICATIONS, AND REGIONAL PERSPECTIVES

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ИНСУЛИНОРЕЗИСТЕНТНОСТЬ: МЕХАНИЗМЫ, КЛИНИЧЕСКОЕ ЗНАЧЕНИЕ И РЕГИОНАЛЬНЫЕ АСПЕКТЫ

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Abstract. Insulin resistance (IR) is a significant pathological condition marked by the impaired response of peripheral tissues such as skeletal muscle, liver, and adipose tissue to insulin, which results in disrupted glucose homeostasis. This dysfunction in insulin action is a key contributor to the development of numerous chronic diseases, including type 2 diabetes mellitus (T2DM), metabolic syndrome, and cardiovascular diseases. The increasing prevalence of IR worldwide has sparked widespread concern in public health, as it plays a pivotal role in the onset and progression of these conditions. In addition to its physical manifestations, IR is also linked to a range of molecular and biochemical alterations, which compound its detrimental effects on overall metabolic health. At the molecular level, the pathogenesis of IR involves a complex interplay of multiple mechanisms, including dysregulated insulin signaling, chronic low-grade inflammation, lipotoxicity, and endoplasmic reticulum (ER) stress. These cytokines promote the phosphorylation of insulin receptor substrates at serine residues, hindering the cascade of events required for effective glucose uptake and utilization. In addition, the accumulation of lipids in non-adipose tissues—termed lipotoxicity—further exacerbates insulin resistance by impairing the function of insulin receptors and signaling molecules, contributing to the progression of metabolic dysfunction. As this complex condition progresses, it is associated with an increased risk of several other serious health issues, including cardiovascular disease, kidney dysfunction, and certain forms of cancer. Consequently, understanding the underlying mechanisms of IR is crucial for the development of targeted therapies and interventions aimed at preventing and managing these associated diseases. Studies from various countries, including Turkey, Russia, and Azerbaijan, provide valuable insights into the prevalence and impact of IR across different populations, highlighting the need for context-specific approaches to diagnosis and treatment.

Аннотация. Инсулиновая резистентность (ИР) является значительным патологическим состоянием, характеризующимся нарушением реакции периферийных тканей, таких как скелетные мышцы, печень и жировая ткань, на инсулин, что приводит к нарушению гомеостаза глюкозы. Этот дисфункциональный процесс в действии инсулина играет ключевую роль в развитии множества хронических заболеваний, включая сахарный диабет 2 типа (СД 2), метаболический синдром и сердечно-сосудистые заболевания. Повышенная распространенность ИР во всем мире вызывает всеобщее беспокойство в области общественного здравоохранения, так как она играет важную роль в начале и прогрессировании этих заболеваний. Кроме физических проявлений, ИР также связана с рядом молекулярных и биохимических изменений, которые усугубляют её пагубное влияние на общий метаболический процесс. На молекулярном уровне патогенез ИР включает сложное взаимодействие нескольких механизмов, таких как дисрегуляция инсулиновых

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сигнализационных путей, хроническое воспаление низкой степени, липотоксичность и стресс эндоплазматического ретикулума (ЭР). Эти цитокины способствуют фосфорилированию субстратов инсулиновых рецепторов на сериновых остатках, что препятствует каскаду событий, необходимых для эффективного усвоения и использования глюкозы. Кроме того, накопление липидов в неадипозных тканях, называемое липотоксичностью, дополнительно усугубляет инсулиновую резистентность, нарушая функцию инсулиновых рецепторов и молекул сигнализации, что способствует прогрессированию метаболической дисфункции. С развитием этого сложного состояния увеличивается риск возникновения нескольких других серьезных заболеваний, таких как сердечно-сосудистые заболевания, дисфункция почек и некоторые формы рака. Следовательно, понимание основных механизмов ИР крайне важно для разработки целевых терапевтических методов и вмешательств, направленных на профилактику и управление этими связанными заболеваниями. Исследования из разных стран, включая Турцию, Россию и Азербайджан, предоставляют ценные данные о распространенности и влиянии ИР на различные популяции, подчеркивая необходимость применения специфичных подходов к диагностике и лечению.

Keywords: diabetes, toxins, insulin, chronic diabetes, glucose.

Ключевые слова: диабет, токсины, инсулин, хронический диабет, глюкоза.

Insulin resistance is a central feature of metabolic disorders, including type 2 diabetes mellitus (T2DM), obesity, and cardiovascular diseases. It is defined by the reduced ability of insulin to exert its effects on glucose uptake and utilization in target tissues such as muscle, adipose tissue, and liver [1].

The growing prevalence of insulin resistance in both developed and developing countries has become a primary concern in public health. While environmental factors such as poor diet, sedentary lifestyle, and obesity have long been associated with the rise in IR, increasing evidence suggests a complex interaction of genetic, epigenetic, and environmental factors contributing to its development. In many cases, insulin resistance occurs silently, without overt symptoms, which is why early detection and intervention are crucial in managing and preventing its long-term consequences. Furthermore, the mechanisms underlying insulin resistance are multifaceted. They involve a range of molecular, cellular, and biochemical processes, including disrupted insulin signaling pathways, chronic low-grade inflammation, lipid accumulation in non-adipose tissues (lipotoxicity), and endoplasmic reticulum (ER) stress. These mechanisms interact and create a cycle that exacerbates the condition, making IR a progressive and challenging disorder to manage.The chronic inflammatory state associated with IR further aggravates the risk of developing related complications such as cardiovascular disease, kidney disease, and certain cancers.

Material and research methods

Molecular Mechanisms of Insulin Resistance.Impaired Insulin Signaling. The insulin signaling pathway involves the activation of the insulin receptor (IR), followed by phosphorylation of insulin receptor substrates (IRS), leading to downstream effects that facilitate glucose uptake. In IR, serine phosphorylation of IRS proteins impairs their function, disrupting the signaling cascade [2].

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Inflammatory Pathways. Chronic low-grade inflammation contributes to IR by activating pro-inflammatory cytokines such as TNF-α and IL-6, which interfere with insulin signaling [11]. These cytokines promote serine phosphorylation of IRS proteins, further impairing insulin action.

Lipotoxicity and Ectopic Fat Accumulation. Excessive accumulation of lipids in non-adipose tissues, such as liver and muscle, leads to lipotoxicity, which impairs insulin signaling pathways [1]. This ectopic fat deposition is associated with mitochondrial dysfunction and oxidative stress, exacerbating IR.

Lipotoxicity refers to the detrimental effects of lipid accumulation in non-adipose tissues, especially when the capacity of adipose tissue to store excess energy is exceeded. Under normal physiological conditions, free fatty acids are safely stored in adipocytes and mobilized during energy demand. However, when lipid intake chronically surpasses storage capacity or when adipose tissue function is impaired, excess lipids are redirected and deposited in tissues not specialized for fat storage, such as skeletal muscle, liver, and pancreatic β-cells.

This ectopic fat deposition disrupts cellular homeostasis by interfering with critical metabolic pathways. Toxic lipid intermediates such as diacylglycerols (DAGs) and ceramides accumulate within cells and impair insulin signaling by inhibiting key molecules in the insulin receptor pathway. These bioactive lipids interfere with insulin-stimulated glucose uptake and promote serine phosphorylation of insulin receptor substrates, leading to insulin resistance.

Furthermore, ectopic lipid accumulation imposes oxidative and endoplasmic reticulum stress, contributing to mitochondrial dysfunction and the activation of inflammatory cascades. In pancreatic β-cells, lipotoxicity reduces insulin secretion capacity and can lead to apoptosis, exacerbating hyperglycemia and metabolic imbalance.

Altogether, lipotoxicity is a central pathological feature linking obesity to insulin resistance and type 2 diabetes, highlighting the importance of proper lipid partitioning and adipose tissue function in metabolic health.

Endoplasmic Reticulum Stress. The endoplasmic reticulum (ER) is a vital cellular organelle responsible for the proper folding, modification, and trafficking of proteins. It also plays key roles in lipid synthesis and calcium homeostasis. Under normal conditions, the ER maintains a finely balanced environment that ensures the correct folding and maturation of newly synthesized proteins. However, various physiological and pathological stimuli—including nutrient overload, oxidative stress, and lipid accumulation—can disrupt ER homeostasis, leading to a condition known as ER stress.

ER stress occurs when the protein-folding capacity of the ER is overwhelmed, resulting in the accumulation of misfolded or unfolded proteins. In response, cells activate a highly conserved signaling network known as the unfolded protein response (UPR). The UPR aims to restore ER homeostasis by halting global protein synthesis, upregulating molecular chaperones to assist in protein folding, and enhancing the degradation of misfolded proteins through ER-associated degradation (ERAD).

Three primary ER stress sensors mediate the UPR: inositol-requiring enzyme 1 (IRE1), protein kinase R-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF6). When activated, these pathways coordinate a complex response to mitigate cellular stress. However, if the ER stress is prolonged or unresolved, the UPR shifts from a protective role to a pro-apoptotic one, triggering programmed cell death via molecules such as C/EBP homologous protein (CHOP) and caspase-12.

In pancreatic β-cells, ER stress is particularly detrimental due to their high demand for insulin biosynthesis. Persistent ER stress in β-cells contributes to dysfunction and apoptosis, accelerating the progression of type 2 diabetes.

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Overall, ER stress is a critical factor in the pathophysiology of metabolic disorders. Targeting ER stress pathways may offer promising therapeutic strategies for preventing or mitigating insulin resistance and its complications.

In the context of insulin resistance and metabolic diseases, ER stress plays a significant role. Chronic overnutrition and lipid overload lead to sustained ER stress in insulin-sensitive tissues like the liver, adipose tissue, and skeletal muscle. This stress impairs insulin signaling by activating c-Jun N-terminal kinase (JNK) and promoting serine phosphorylation of insulin receptor substrates. Moreover, ER stress is closely linked with inflammation, mitochondrial dysfunction, and oxidative stress—creating a vicious cycle that exacerbates insulin resistance and metabolic decline

The endoplasmic reticulum (ER) plays a crucial role in protein folding and secretion. ER stress, resulting from the accumulation of misfolded proteins, activates the unfolded protein response, which can inhibit insulin signaling pathways [1].

Clinical Implications. IR is a precursor to several metabolic disorders. In T2DM, IR leads to compensatory hyperinsulinemia, eventually resulting in β-cell dysfunction and hyperglycemia. In cardiovascular diseases, IR contributes to endothelial dysfunction, hypertension, and atherogenesis [3].

Therapeutic Strategies.Lifestyle Modifications. Dietary interventions and physical activity are first-line strategies to improve insulin sensitivity. Exercise enhances glucose uptake in skeletal muscles independently of insulin, while dietary modifications can reduce adiposity and inflammation [1].

Pharmacological Interventions. Medications such as metformin improve insulin sensitivity by activating AMP-activated protein kinase (AMPK), which enhances glucose uptake and fatty acid oxidation. Thiazolidinediones, another class of insulin sensitizers, act by activating peroxisome proliferator-activated receptor gamma (PPARγ) [2].

Results and discussion

Regional Perspectives. Research in Turkey has highlighted the prevalence of IR in obese populations and its association with metabolic syndrome components. A study by Demir et al. (2019) found a significant correlation between IR and elevated inflammatory markers in Turkish adults [4].

In Russia, studies have focused on the genetic predisposition to IR and its impact on public health. Ivanov et al. (2020) reported a high prevalence of IR among individuals with a family history of T2DM, emphasizing the need for early screening and intervention.

Azerbaijani research has explored the relationship between dietary patterns and IR. Aliyev et al. (2018) demonstrated that traditional diets rich in refined carbohydrates are associated with increased IR risk, suggesting dietary modification as a preventive strategy [6].

Conclusion

Insulin resistance (IR) is a multifactorial metabolic disorder that serves as a core pathogenic mechanism for several chronic diseases, including type 2 diabetes mellitus (T2DM), cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), and polycystic ovary syndrome (PCOS). It involves a complex network of biochemical and molecular disruptions—ranging from impaired insulin receptor signaling and lipotoxicity to oxidative stress and endoplasmic reticulum dysfunction—that collectively disturb systemic glucose and lipid homeostasis [7].

The heterogeneity of IR pathophysiology necessitates a comprehensive and integrative approach to prevention and management. Therapeutic strategies include lifestyle interventions such as diet and exercise, pharmacologic agents like metformin and thiazolidinediones, and emerging

treatments targeting inflammatory pathways and cellular stress responses [8]. Furthermore, public health initiatives that promote early screening and risk factor mitigation are essential to curb the rising prevalence of IR-related disorders. Incorporating findings from Turkish, Russian, and Azerbaijani literature expands the global perspective on IR. Regional studies have provided unique insights into dietary patterns, genetic polymorphisms, and cultural health practices that influence the development and progression of insulin resistance [9-11].

These localized perspectives are crucial for developing culturally sensitive interventions and public health strategies that address the specific needs of various populations. In conclusion, insulin resistance is not only a medical concern but also a public health priority. Addressing it through multidisciplinary research, personalized medicine, and regional collaboration holds promise for improving metabolic health outcomes worldwide. Insulin resistance is a multifaceted condition with significant implications for metabolic health. Understanding its molecular mechanisms and clinical consequences is essential for developing effective prevention and treatment strategies. Incorporating regional research findings enriches our comprehension of IR and informs culturally tailored interventions.

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