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eISSN 2450-3118 · Open Access · Peer-reviewed

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JĘDRYSIAK, Joanna, STOLECKA, Greta, GŁODZIK, Paulina, KOBIAŁKA, Weronika, ESTREICHER, Agata, KOLANKO, Magdalena, LEGASZEWSKA, Maria, KOSIDŁO, Patrycja, MIKÓŁKA, Karolina and LELONKIEWICZ, Martyna. Obesity, Insulin Resistance and Type 2 Diabetes Mellitus - Pathophysiological Mechanisms and Exercise-Based Strategies. *Quality in Sport*. 2026;77:75984. <https://doi.org/10.12775/QS.2026.77.75984>

ARTICLE TIMELINE

Received: 09.09.2026. Accepted: 14.09.2026. Published: 28.09.2026.

The journal has been awarded 20 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32553). Unique Journal Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences). Punkty Ministerialne z 2019 – aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych). © The Authors 2026.

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Obesity, Insulin Resistance and Type 2 Diabetes Mellitus - Pathophysiological Mechanisms and Exercise-Based Strategies

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Abstract

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by chronic hyperglycemia resulting from insulin resistance and progressive pancreatic β -cell dysfunction. Its pathogenesis involves multiple interconnected mechanisms affecting skeletal muscle, liver, adipose tissue, and systemic metabolic regulation. Obesity, particularly visceral adiposity, plays a central role in the development of insulin resistance through lipotoxicity, mitochondrial dysfunction, endoplasmic reticulum stress, and chronic low-grade inflammation. These mechanisms disrupt insulin signaling and contribute to progressive metabolic dysfunction. Physical activity represents one of the most effective non-pharmacological interventions in both prevention and treatment of T2DM. Regular exercise improves glucose uptake in skeletal muscle, enhances insulin sensitivity, reduces visceral adipose tissue, and improves overall metabolic flexibility. Current recommendations emphasize at least 150 minutes of moderate-intensity aerobic exercise per week combined with resistance training performed 2–3 times weekly. This narrative review summarizes current knowledge regarding the molecular basis of

insulin resistance and highlights the therapeutic role of physical activity as a key strategy in the management of T2DM.

Keywords: type 2 diabetes mellitus, insulin resistance, obesity, physical activity, skeletal muscle, lipotoxicity

1. Introduction

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia caused by impaired insulin secretion, insulin resistance, or both. Type 2 diabetes mellitus (T2DM) is the most prevalent form and represents one of the major global public health challenges. Its incidence continues to rise worldwide due to increasing rates of obesity, sedentary lifestyle, population aging, dyslipidemia, hypertension, and genetic predisposition. [1]

T2DM develops gradually and is strongly associated with insulin resistance, a condition in which peripheral tissues demonstrate reduced responsiveness to insulin. Initially, pancreatic β -cells compensate by increasing insulin secretion; however, progressive β -cell dysfunction eventually leads to persistent hyperglycemia and overt diabetes. [2]

The pathophysiology of T2DM extends beyond glucose metabolism alone and involves a complex network of interactions between adipose tissue, skeletal muscle, and liver. Obesity, particularly visceral fat accumulation, plays a central role in initiating these disturbances through chronic inflammation, excess free fatty acid release, mitochondrial dysfunction, and lipotoxicity. [3]

Physical activity has become increasingly recognized as a fundamental therapeutic strategy in T2DM management. Exercise improves insulin sensitivity, reduces adiposity, enhances glucose uptake, and decreases cardiometabolic risk. Because of its broad metabolic effects, physical activity should be considered a cornerstone of both prevention and treatment. [1]

The aim of this narrative review is to summarize the mechanisms linking obesity to insulin resistance and multiorgan metabolic dysfunction in T2DM, with particular emphasis on the role of physical activity as a key therapeutic intervention.

2. Methods

This narrative review was conducted to summarize current knowledge regarding the pathophysiology of type 2 diabetes mellitus, with particular emphasis on insulin resistance, inter-organ metabolic interactions, and therapeutic approaches focused on physical activity.

A literature search was performed using the PubMed database for articles published in English between 2010 and 2025. The search strategy included combinations of the following keywords: type 2 diabetes mellitus, insulin resistance, obesity, lipotoxicity, skeletal muscle insulin

resistance, hepatic insulin resistance, mitochondrial dysfunction, endoplasmic reticulum stress, inflammation, exercise therapy, physical activity, and insulin sensitivity.

Priority was given to peer-reviewed original research articles, systematic reviews, meta-analyses, and position statements from recognized scientific societies such as the American Diabetes Association (ADA) and the American College of Sports Medicine (ACSM). Studies were selected based on relevance to molecular mechanisms of insulin resistance and the clinical effects of exercise interventions.

Articles focusing exclusively on type 1 diabetes, gestational diabetes, or unrelated endocrine disorders were excluded. A total of 68 publications were included in the final review.

The selected literature was critically analyzed and synthesized in a narrative format to integrate molecular, cellular, and organ-level mechanisms into a unified pathophysiological model.

3. Physiology of Insulin Action

Insulin is a peptide hormone secreted by pancreatic β -cells in response to elevated blood glucose concentrations. Its primary physiological role is the maintenance of glucose homeostasis. Glucagon exerts opposite metabolic effects by stimulating hepatic glucose production during fasting. [2]

Insulin exerts its effects through a transmembrane tetrameric receptor composed of two extracellular α -subunits and two β -subunits possessing intrinsic tyrosine kinase activity. Insulin binding induces conformational changes and autophosphorylation of the β -subunits, leading to activation of downstream signaling pathways. Two major cascades are subsequently triggered: the PI3K/AKT pathway, which regulates glucose uptake, glycogen synthesis, lipid and protein metabolism, and the MAPK pathway, which mediates cellular proliferation, growth, and differentiation. [4]

Insulin acts mainly on skeletal muscle, liver, and adipose tissue. In skeletal muscle, insulin stimulates glucose uptake via translocation of GLUT4 transporters to the cell membrane, promotes glycogen synthesis, and enhances protein synthesis while inhibiting proteolysis.

In the liver, insulin suppresses gluconeogenesis and glycogenolysis while stimulating glycogen storage and lipogenesis. In adipose tissue, insulin inhibits lipolysis and promotes triglyceride storage, thereby reducing circulating free fatty acids. [5]

These organs function as an integrated metabolic network. Disturbances in one tissue may directly affect the others through altered substrate availability, hormonal signaling, and inflammatory mediators, contributing to systemic insulin resistance. [6]

4. Obesity and Insulin Resistance

Obesity is defined as excessive body fat accumulation that negatively affects health and is commonly diagnosed using body mass index ($\text{BMI} \geq 30 \text{ kg/m}^2$). It is mainly caused by imbalanced energy intake and expenditure due to a sedentary lifestyle coupled with overnutrition. Excess nutrients are stored in adipose tissue in the form of triglycerides. [7,8]

Under conditions of excessive energy intake, particularly from diets rich in fats and carbohydrates, an increased influx of glucose into hepatocytes and adipocytes occurs. Excess glucose that is neither utilized for energy production nor further stored as glycogen is redirected toward lipogenic pathways. [9]

Obesity is one of the main risk factors for insulin resistance and type 2 diabetes mellitus (T2DM), especially when fat is stored viscerally. White adipose tissue can be classified into

two major depots: subcutaneous adipose tissue and visceral adipose tissue, the latter of which accumulates around internal organs. [10]

Adipose tissue is not only an energy store but also an active endocrine organ involved in metabolism and inflammation. In obesity, particularly visceral obesity, adipocytes become enlarged and less sensitive to insulin. They release more free fatty acids (FFAs) and pro-inflammatory cytokines such as TNF- α and IL-6, while adiponectin levels decrease. This promotes chronic low-grade inflammation and disrupts insulin signaling. [11]

As a result, glucose uptake in skeletal muscle decreases, while in the liver insulin is less able to suppress gluconeogenesis, leading to increased hepatic glucose production. Elevated FFAs further worsen insulin resistance and promote fatty liver. Visceral fat is more harmful than subcutaneous fat because it is more metabolically active and strongly associated with cardiometabolic complications. [12]

5. Cellular Mechanisms in Insulin Resistance

5.1 Insulin Resistance

Insulin resistance (IR) is defined as a reduced biological response of target tissues—primarily skeletal muscle, liver, and adipose tissue—to normal or even elevated insulin concentrations, resulting in impaired glucose uptake, utilization, and storage. Under physiological conditions, insulin promotes glucose transport into cells, inhibits hepatic glucose production, suppresses lipolysis, and supports protein and lipid synthesis. In insulin resistance, these effects become progressively impaired, leading to disturbances in both carbohydrate and lipid metabolism.

In the early stage, pancreatic β -cells compensate by increasing insulin secretion, resulting in compensatory hyperinsulinemia, which may maintain near-normal glycemic control for years. This phase often corresponds to prediabetes or clinically silent insulin resistance. However, prolonged exposure to glucotoxicity, lipotoxicity, oxidative stress, and secretory overload gradually leads to β -cell dysfunction and reduced insulin secretion. Once β -cells can no longer compensate for the degree of insulin resistance, fasting and postprandial glucose levels rise, leading to overt type 2 diabetes mellitus (T2DM). [5]

5.2 Mitochondrial Dysfunction and Endoplasmic Reticulum Stress

Mitochondria in obese individuals exhibit substantial structural and functional alterations compared with those in lean individuals, reflecting the association between overnutrition and mitochondrial dysfunction. Obesity has been associated with impaired mitochondrial biogenesis, altered mitochondrial dynamics, increased lipid peroxidation, and dysregulated fatty acid oxidation, leading to the accumulation of lipotoxic intermediates, including diacylglycerols and ceramides. Excess substrate availability enhances mitochondrial production of reactive oxygen species (ROS) and hydrogen peroxide (H_2O_2), resulting in oxidative damage to mitochondrial DNA, lipid membranes, proteins, and respiratory chain enzymes. Consequently, oxidative stress and mitochondrial dysfunction promote the accumulation of oxidized intracellular components and trigger pro-inflammatory signaling pathways that contribute to the development of insulin resistance. [13]

Excess nutrient supply also induces endoplasmic reticulum (ER) stress through protein misfolding and disrupted cellular homeostasis. Chronic activation of ER stress pathways stimulates inflammatory signaling and impairs insulin receptor signaling, further worsening insulin resistance. [13]

5.3 Lipotoxicity

Lipotoxicity refers to the pathological accumulation of lipids in non-adipose tissues such as skeletal muscle, liver, pancreas, heart, and kidneys, where fat storage is normally limited. It occurs when the storage capacity of adipose tissue is exceeded, most commonly in obesity and chronic overnutrition. As a result, excess free fatty acids (FFAs) accumulate in other organs, leading to metabolic dysfunction.

The most harmful effects are caused by toxic lipid intermediates such as ceramides and diacylglycerols (DAGs), which impair insulin signaling pathways and reduce insulin sensitivity. They also promote oxidative stress, inflammation, and cellular damage. In pancreatic β -cells, prolonged lipid exposure may lead to apoptosis and reduced insulin secretion.

In the liver, lipotoxicity contributes to hepatic insulin resistance and non-alcoholic fatty liver disease (NAFLD). In skeletal muscle, it reduces glucose uptake, while in the pancreas it impairs insulin production. In the heart and kidneys, chronic lipid overload may contribute to cardiomyopathy and diabetic kidney disease. Therefore, lipotoxicity is one of the major mechanisms linking obesity with multiorgan dysfunction and progression to type 2 diabetes mellitus (T2DM). [14]

6. Tissue-Specific Insulin Resistance

6.1 Skeletal Muscle

Skeletal muscle is the primary site of insulin-mediated glucose disposal and therefore plays a central role in the development of insulin resistance. Reduced insulin responsiveness impairs glucose uptake and glycogen synthesis, largely through defective proximal insulin signaling and impaired GLUT4 translocation. Intramyocellular lipid accumulation, dysregulated fatty acid oxidation, and mitochondrial dysfunction further decrease metabolic flexibility and impair the ability to switch between lipid and glucose utilization. Accumulation of lipotoxic intermediates, including diacylglycerols and ceramides, activates stress-related kinases, thereby promoting inflammatory signaling and antagonizing insulin action. In addition, obesity-associated inflammation in skeletal muscle, characterized by increased cytokine production and immune cell infiltration, further exacerbates defects in insulin signaling and contributes to systemic metabolic dysfunction. [15]

6.2 Adipose Tissue

One of the key actions of insulin is the suppression of lipolysis in adipose tissue. In the presence of insulin resistance, lipolysis is enhanced, leading to an increased plasma concentration of triglyceride breakdown products (free fatty acids and glycerol) released from adipose tissue.

These metabolites are taken up by hepatocytes, where they stimulate hepatic glucose production through the regulation of enzymatic pathways or by serving directly as gluconeogenic substrates (as in the case of glycerol).

Furthermore, when free fatty acid levels exceed the oxidative capacity of tissues, the surplus is re-esterified into triglycerides in various organs, resulting in ectopic lipid accumulation and contributing to the development of metabolic disorders. [16]

6.3 Liver

Hepatic insulin resistance is characterized by impaired suppression of gluconeogenesis and glycogenolysis, leading to excessive hepatic glucose production and fasting hyperglycemia. Defects in insulin signaling, promote the persistent expression of gluconeogenic enzymes, including glucose-6-phosphatase and phosphoenolpyruvate carboxykinase. Simultaneously, insulin resistance disrupts glycogen synthesis and diminishes hepatic glycogen storage, contributing to abnormal hepatic glucose metabolism.

Despite impaired regulation of glucose homeostasis, hepatic lipogenesis frequently remains preserved or even enhanced, a phenomenon often referred to as selective hepatic insulin resistance. Chronic overnutrition, together with increased delivery of free fatty acids from dysfunctional adipose tissue, promotes hepatic triglyceride accumulation and the development of non-alcoholic fatty liver disease (NAFLD). In addition, excessive lipid influx and dysregulated fatty acid metabolism favor the accumulation of lipotoxic intermediates, including diacylglycerols and ceramides, which further impair insulin signaling pathways and exacerbate hepatic steatosis. Mitochondrial dysfunction, oxidative stress, and low-grade inflammation further contribute to hepatocellular metabolic disturbances and amplify systemic insulin resistance. [17]

7. Integrated Model of Insulin Resistance

Nutrient oversupply represents the central mechanism linking obesity, insulin resistance, and multiorgan dysfunction.

Excess caloric intake promotes accumulation of free fatty acids and toxic lipid intermediates, triggering mitochondrial dysfunction, oxidative stress, ER stress, and chronic inflammation. These mechanisms interact in a self-reinforcing cycle that leads to progressive impairment of insulin signaling in skeletal muscle, liver, and adipose tissue.

As insulin resistance worsens, β -cell compensation becomes insufficient, resulting in persistent hyperglycemia and progression to clinically overt T2DM. [18]

8. Role of Physical Activity in Prevention and Treatment of T2DM

8.1 Exercise and Insulin Sensitivity

Management of type 2 diabetes mellitus should place strong emphasis on regular physical activity as a key therapeutic component. Exercise increases glucose uptake in skeletal muscle through both insulin-dependent and insulin-independent pathways, primarily by stimulating GLUT4 translocation and improving mitochondrial efficiency. Regular physical activity enhances insulin sensitivity and reduces peripheral insulin resistance, which directly improves glycemic control.

Even short-term aerobic exercise has been shown to improve whole-body insulin responsiveness. Long-term training additionally supports better metabolic flexibility and reduces the progression of prediabetes to overt T2DM. These effects are particularly important in individuals with obesity and visceral adiposity, where insulin resistance is strongly pronounced. [19]

8.2 Aerobic and Resistance Training

Current guidelines from the American Diabetes Association (ADA) and the American College of Sports Medicine (ACSM) recommend at least 150 minutes of moderate-intensity aerobic exercise per week, performed over at least three days, with no more than two consecutive days without physical activity.

Aerobic exercise such as walking, cycling, swimming, or jogging improves cardiovascular fitness, enhances glucose utilization, and reduces fasting plasma glucose levels. In addition to aerobic training, resistance exercise should be performed 2–3 times per week.

Resistance training improves skeletal muscle mass, increases resting metabolic rate, and supports long-term glucose disposal by expanding the main tissue responsible for glucose uptake. Combined aerobic and resistance training provides the most beneficial metabolic outcomes and should be considered the optimal exercise strategy for patients with T2DM. [20]

8.3 Exercise and Body Composition

Regular physical activity contributes significantly to the reduction of total body fat and, most importantly, visceral adipose tissue, which is closely associated with insulin resistance and chronic low-grade inflammation.

Decreased fat mass leads to lower secretion of pro-inflammatory cytokines and reduced release of free fatty acids from adipose tissue. This improves adipose tissue endocrine function and decreases lipotoxicity in skeletal muscle and liver.

Improved body composition results in enhanced insulin sensitivity, better glucose metabolism, and lower cardiometabolic risk. Exercise-induced reduction of visceral obesity is therefore one of the most important mechanisms in preventing progression toward T2DM. [21]

8.4 Additional Benefits of Physical Activity

Physical activity also improves cardiovascular health, which is particularly important in patients with T2DM due to their elevated risk of hypertension, atherosclerosis, myocardial infarction, and stroke. Regular exercise improves endothelial function, lowers blood pressure, improves lipid profile, and reduces systemic inflammation.

Furthermore, exercise has important psychological benefits. It reduces symptoms of anxiety, stress, and depression, which frequently accompany chronic metabolic diseases and may negatively affect treatment adherence.

Physical activity also improves sleep quality, physical performance, functional independence, and overall quality of life. These multidimensional benefits make exercise one of the most comprehensive therapeutic interventions in modern diabetes management. [22]

8.5 Clinical Implications

Physical activity should be considered not only an adjunctive intervention but also a central therapeutic strategy in both prevention and treatment of type 2 diabetes mellitus. Exercise prescription should be individualized based on patient age, baseline physical fitness, cardiovascular risk, obesity severity, and the presence of comorbidities.

Healthcare professionals should actively promote structured lifestyle interventions as early as possible, especially in patients with prediabetes and metabolic syndrome. Long-term adherence to regular exercise remains one of the most effective approaches for reducing disease

progression, improving metabolic outcomes, and preventing long-term diabetic complications. [23]

9. Limitations of the Review

This review has several limitations. As a narrative review, it does not follow the strict methodological framework of a systematic review and may therefore be associated with selection bias. Although priority was given to high-quality studies, meta-analyses, and current clinical recommendations, some relevant publications may not have been included.

Additionally, this review focuses primarily on the metabolic mechanisms of insulin resistance and the therapeutic role of physical activity, while pharmacological treatment strategies were discussed only briefly. Future studies should evaluate the combined effects of exercise interventions and modern antidiabetic therapies in various clinical populations.

10. Conclusion

Type 2 diabetes mellitus is a complex metabolic disorder resulting from the interaction of insulin resistance, obesity, lipotoxicity, mitochondrial dysfunction, and chronic low-grade inflammation across multiple organs.

Visceral adiposity plays a central role in the initiation and progression of metabolic dysfunction by promoting impaired insulin signaling and progressive β -cell failure. Skeletal muscle and liver remain the key target organs in this process, and disturbances in their metabolic regulation strongly contribute to hyperglycemia and disease progression.

Regular physical activity represents one of the most effective non-pharmacological strategies in both prevention and treatment of T2DM. Exercise improves insulin sensitivity, increases skeletal muscle glucose uptake, reduces visceral fat mass, and improves overall metabolic flexibility.

Understanding the integrated mechanisms of insulin resistance provides a strong foundation for effective therapeutic strategies. Lifestyle intervention, particularly structured physical activity, should remain a cornerstone of modern diabetes care, prevention, and long-term metabolic health.

Disclosure

Supplementary Materials: Not applicable.

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All authors have read and agreed with the published version of the manuscript.

Funding:

This study has not received any external funding.

Institutional Review Board Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

Not applicable.

Acknowledgements:

Not applicable.

Conflict of Interest:

The authors declare that there are no financial or personal relationships with other people or organizations that could inappropriately influence (bias) their work.

AI:

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

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