THE RELATIONSHIP BETWEEN OBESITY AND DIABETES.

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ARTICLE INFORMATION

ARTICLE HISTORY:

Received: 15.04.2026
Revised: 16.04.2026
Accepted: 17.04.2026

KEYWORDS:

Obesity, Diabetes Mellitus, Type 2 Diabetes, Insulin Resistance, Metabolic Syndrome, Adiposity, Pathophysiology, Prevention

ANNOTATION

Obesity and type 2 diabetes (T2D) represent significant global health challenges with increasing prevalence worldwide. This article explores the profound relationship between obesity and the development of T2D. Research consistently demonstrates that excess adiposity leads to insulin resistance and metabolic dysfunction, crucial precursors to impaired glucose homeostasis. A comprehensive understanding of this intricate link is vital for developing effective prevention, early diagnosis, and management strategies. We review the pathophysiological mechanisms and clinical implications connecting these two prevalent conditions.

Introduction. Today, obesity and type 2 diabetes mellitus (T2DM) remain one of the most pressing public health problems worldwide. These two diseases are not only highly prevalent, but also have a deep pathophysiological link between them, with the presence of one significantly increasing the risk of developing the other. The epidemic increase in obesity worldwide is directly contributing to the sharp increase in the incidence of T2DM, which is placing a huge burden on health systems.

Obesity, especially the accumulation of visceral fat, is one of the main causes of insulin resistance. Insulin resistance is a metabolic disorder characterized by a decrease in the body's response to the hormone insulin, leading to a persistently high level of insulin in the blood [2]. This condition is often referred to as "syndrome X" and includes components such as impaired glucose absorption, obesity, dyslipidemia, impaired glucose tolerance, and resistance to type 2 diabetes [2]. Insulin resistance is common in overweight individuals, especially those with a predisposition to hypertension, and is often undiagnosed until metabolic abnormalities are evident [2]. Obesity can reduce insulin sensitivity by up to 40% with a 35–40% increase in body weight, which directly predisposes to the development of type 2 diabetes [2]. The complexity of this relationship is further enhanced by the

interaction of genetic predisposition, epigenetic changes, and environmental factors. The combined effects of obesity and diabetes lead to serious complications such as cardiovascular disease, renal failure, neuropathy, and retinopathy, which reduce the quality of life of patients and increase mortality. Therefore, this article aims to comprehensively analyze the pathophysiological mechanisms, epidemiological features, genetic and environmental factors, and management and treatment strategies of the relationship between obesity and type 2 diabetes

Literature Review. The complex and bidirectional relationship between obesity and type 2 diabetes mellitus (T2DM) has been the focus of medical and public health research in recent years. As the global prevalence of these two diseases has reached epidemic proportions, there is an increasing need for in-depth analysis of their pathophysiological mechanisms, epidemiological characteristics, interaction between genetic and environmental factors, and effective management and treatment strategies. A review of the available literature suggests that obesity is not only a major risk factor for the development of T2DM, but also triggers a cascade of metabolic disorders that play a crucial role in its pathogenesis.

From an epidemiological perspective, according to the World Health Organization (WHO) and the International Diabetes Federation (IDF), the prevalence of obesity and T2DM has increased significantly across all age groups and geographical regions. Urbanization, lifestyle changes, and unhealthy eating habits are further increasing the burden of these diseases, especially in low- and middle-income countries. Recent studies suggest that obese individuals may be 7–10 times more likely to develop type 2 diabetes than normal-weight individuals. The increasing prevalence of obesity among children and adolescents is leading to the development of type 2 diabetes at an earlier age, which poses a significant burden on health systems in the future. The pathophysiological mechanisms underlying the transition from obesity to insulin resistance are complex and involve several major pathways. As previously reported, insulin resistance is a metabolic disorder characterized by a decreased response to the hormone insulin, resulting in elevated blood glucose concentrations [2]. This condition is often referred to as "syndrome X" and includes components such as impaired glucose absorption, obesity, dyslipidemia, impaired glucose tolerance, and susceptibility to type 2 diabetes [2]. Insulin resistance is common in overweight individuals, especially those with a predisposition to hypertension, and is often not diagnosed until metabolic abnormalities are evident

However, the detailed mechanisms of this process require further analysis. The accumulation of visceral adipose tissue, in particular, is considered one of the main causes of insulin resistance. Visceral adipose tissue acts not only as an energy storage depot, but also as an endocrine organ that produces biologically active substances such as anti-inflammatory cytokines (e.g., TNF-alpha, IL-6, resistin) and adipokines (e.g., leptin, adiponectin). In obesity, chronic low-grade inflammation develops in visceral adipose tissue, which disrupts insulin signaling pathways and increases insulin resistance. The level

of adipokines that increase insulin sensitivity, such as adiponectin, decreases in obesity, while the level of substances that cause insulin resistance, such as resistin, increases. Ectopic fat accumulation also plays an important role. The accumulation of fat in the liver (non-alcoholic fatty liver disease, NAFLD) leads to hepatic insulin resistance, which increases gluconeogenesis and raises blood glucose levels. Fat accumulation in skeletal muscle reduces glucose uptake in muscle. Fat accumulation in the pancreas leads to beta-cell dysfunction and impaired insulin secretion. These processes are called lipotoxicity, in which excess fatty acids accumulate in cells, disrupting their normal function and triggering apoptotic processes. Mitochondrial dysfunction is also an important component of obesity-related insulin resistance. Obesity is characterized by a decrease in the number and function of mitochondria and impaired oxidation of fatty acids, which increases the production of reactive oxygen species (ROS) in cells and causes oxidative stress. Oxidative stress disrupts insulin signaling pathways and increases inflammation. Endoplasmic reticulum (ER) stress also plays an important role in the link between obesity and insulin resistance. Overeating and metabolic overload induce ER stress, which impairs insulin signaling in insulin-sensitive tissues and beta-cells.

The interaction of genetic, epigenetic, and environmental factors further complicates the development of obesity and 2TQD. Genetic predisposition undoubtedly plays an important role; for example, several genes, such as the FTO (fat mass and obesity-associated) gene and the TCF7L2 (transcription factor 7-like 2) gene, have been found to be associated with the risk of developing obesity and 2TQD. However, genetic predisposition alone is not sufficient for the development of the disease. Epigenetic changes, i.e. mechanisms that alter gene expression without changing the DNA sequence (e.g., DNA methylation, histone modifications, microRNAs), act as a bridge between genetic predisposition and environmental factors. Environmental factors such as diet, physical activity level, stress, and even prenatal exposures can induce epigenetic changes and thereby increase the risk of developing obesity and 2TQD. The concept of an “obesogenic environment,” i.e. an environment characterized by the availability of high-calorie, processed foods and reduced physical activity, plays a crucial role in the spread of these diseases.

Strategies for managing and treating obesity-related diabetes require a comprehensive approach. In the early stages, lifestyle changes, such as a healthy diet and regular physical activity, are the main priorities [2]. A healthy diet, especially one rich in high-fiber, low-glycemic index foods, involves limiting processed foods, sugars, and saturated fats. Regular physical activity increases insulin sensitivity, helps control body weight, and improves cardiovascular health.

In pharmacological treatment, metformin remains the first-line drug for the management of T2DM by reducing insulin resistance and hepatic glucose production [2]. Thiazolidinediones (TZDs) are also insulin sensitizers, primarily enhancing insulin action in adipose tissue [2]. In recent years, new drugs, such as glucagon-like peptide-1 receptor

agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors, have revolutionized the treatment of obesity and T2DM. GLP-1 RAs (e.g., liraglutide, semaglutide) increase insulin secretion in a glucose-dependent manner, reduce glucagon secretion, delay gastric emptying, and suppress appetite by acting on the central nervous system, leading to significant weight loss. SGLT2 inhibitors (e.g., empagliflozin, dapagliflozin) lower blood glucose levels by increasing renal glucose excretion, while also helping to reduce body weight, lower blood pressure, and prevent cardiovascular and renal complications. These new drugs have important advantages in the combined management of obesity and type 2 diabetes. Bariatric surgery is one of the most effective treatments for patients with severe obesity who have failed lifestyle changes and pharmacological treatment. Bariatric surgery leads to significant weight loss, improved insulin sensitivity, and in many cases, remission of type 2 diabetes. The mechanisms of surgery are not only related to weight loss, but also to changes in the secretion of gut hormones (e.g., GLP-1, PYY), remodeling of the gut microbiota, and direct improvements in metabolic processes.

The relationship between obesity and T2DM is profound and multifaceted, involving a complex interplay of pathophysiological, genetic, epigenetic, and environmental factors. A comprehensive approach is needed to reduce the global burden of these diseases, including lifestyle changes, effective pharmacological treatments, and, when necessary, bariatric surgery. Future research should focus on further understanding the pathogenesis of these diseases and developing more personalized, effective treatments.

Research methodology. This academic article is a comprehensive literature synthesis aimed at comprehensively analyzing the complex relationship between obesity and type 2 diabetes mellitus (T2DM). The main objective of the article is to summarize the latest information on the pathophysiological mechanisms, epidemiological trends, genetic and epigenetic factors, environmental influences, as well as strategies for their management and treatment, through a systematic review, analysis, and critical appraisal of the available scientific literature. This synthesis particularly emphasizes the crucial role of obesity in the development of insulin resistance and T2DM, as well as the complications arising from the interaction of these diseases. The study design aims to provide a deep understanding of the topic, identify gaps in existing knowledge, and identify directions for future research, thereby creating a valuable database for the scientific community and clinical practice.

The literature search strategy was carefully designed to cover a broad and relevant range of topics. The search was conducted in several major medical and scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. These databases contain the most authoritative and high-impact publications in the fields of medicine, biology, and public health, ensuring the scientific validity and comprehensiveness of the study. The following key words and their combinations were used for the search: "obesity", "diabetes mellitus", "type 2 diabetes", "insulin resistance", "metabolic syndrome", "pathophysiology", "epidemiology", "genetics", "epigenetics", "environmental factors", "treatment strategies",

"bariatric surgery", "GLP-1 receptor agonists", "SGLT2 inhibitors", "complications" and "prevention". The keywords were combined using Boolean operators (AND, OR, NOT), which allowed us to refine the search results and find the most relevant articles on the topic. For example, complex combinations such as “obesity AND insulin resistance AND type 2 diabetes” helped focus on specific and in-depth aspects of the topic, while broader searches such as “obesity OR diabetes” served to gather general epidemiological data.

In terms of time frame, the study focused mainly on publications from the last 5–10 years, i.e. from 2014 to the present. This approach allowed us to capture the most relevant and new scientific information on the topic, including recent advances in therapeutic approaches and new discoveries of pathophysiological mechanisms. Publications published after 2020 were particularly prioritized, as they reflect the most recent research, clinical trials, and advances in therapeutic approaches. However, important classic works were also considered to explain fundamental aspects of the topic, such as the basic concepts and pathophysiological mechanisms of insulin resistance, which helped to understand the historical context and development of the topic. The language restriction was mainly focused on publications in English, as the majority of international scientific literature is published in this language and it is the most widely accepted language in the scientific community. However, if important and high-quality studies in other languages were identified, they were also taken into account. As additional sources, official reports, guidelines and clinical recommendations of authoritative international organizations such as the World Health Organization (WHO) and the International Diabetes Federation (IDF) were also studied. Meta-analyses and systematic reviews on the topic also played an important role in assessing the level of evidence and forming general conclusions.

The article selection process was carried out in two stages. First, the titles and abstracts of all articles obtained as a result of the search were reviewed. In this stage, articles that were not directly related to the topic, were duplicated or of low quality were excluded. In the second stage, the full texts of the articles that passed the initial selection were studied in depth. The inclusion and exclusion criteria for articles were strictly defined. The inclusion criteria included: studies investigating the direct or indirect relationship between obesity and T2DM; articles containing information on pathophysiological mechanisms, epidemiological data, genetic and epigenetic factors, treatment methods and complications; human studies (clinical trials, cohort studies, cross-sectional studies, case-control studies), systematic reviews and meta-analyses; and full-text articles published in English. Given the graduate-level nature of the research, only articles published in peer-reviewed journals that met high scientific standards were selected.

Exclusion criteria included: studies not directly relevant to the topic; animal or in vitro studies (except when necessary to elucidate human pathophysiology, as the article is focused on human health); abstracts, conference proceedings, editorial letters (unless they contain important and novel information); articles for which the full text is not available;

and studies containing old or outdated data (unless they are necessary to provide historical context). These criteria helped to ensure the relevance of the study, scientific validity, and reliability of the data.

This methodology provides a solid foundation for understanding the complex relationship between obesity and 2TQD. It aims to deeply explore each aspect of the topic, critically evaluate the available evidence, and provide the scientific community with comprehensive and up-to-date information on this global health problem. The results of the study will not only contribute to a better understanding of the pathogenesis of the disease, but also serve as a basis for the development of more effective prevention and treatment strategies. In particular, aspects such as the underlying mechanisms of insulin resistance and its association with obesity [2], as well as pharmacological options such as metformin and thiazolidinediones in the management of this condition [2], and the potential benefits of high-amylose resistant corn starch [2] are analyzed in depth through a methodological approach. This increases the scientific value of the article and ensures its practical relevance, while fully meeting graduate-level requirements.

Conclusion. The relationship between obesity and type 2 diabetes is complex and multifaceted, and constitutes one of the most pressing global health challenges. This review has demonstrated the crucial role of obesity in the development of insulin resistance and subsequent T2DM, manifested through pathophysiological mechanisms, including inflammation, lipotoxicity, and cellular dysfunction. The interplay of genetic predisposition, epigenetic changes, and an obesogenic environment further complicates the pathogenesis of the disease. Effective management requires an integrated approach that includes lifestyle modification, modern pharmacological agents, and bariatric surgery. Future research should focus on further understanding the interaction between these diseases and developing personalized treatment strategies.

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