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Molecular Basis of Diabetes and Obesity Interactions: A Mini-Review

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Abstract:

Diabetes and obesity are the most common comorbidities. Like obesity, type 2 diabetes is a major public health challenge. Indeed, diabetes poses a "global health threat". The urgency of this situation is evident when one considers the high prevalence of obesity alongside these increasing numbers of diabetes cases, as it has been established that obesity is the basis of insulin resistance. Obesity involves genetic, socioeconomic, and environmental factors, and 45-75% of the susceptibility to obesity is heritable. Since diabetes arises from complex interactions between genetic and environmental factors (including diet, physical activity, and drugs), it is unsurprising that susceptibility to diabetes is also quite high. The homeostatic regulation of blood glucose in vertebrates reveals an intricate metabolism of glucose and involves numerous genes. The lack of physical activity and regular diet, alongside other factors, results in an imbalance of this complex metabolism, leading to obesity-induced diabetes. This raises the question of the genetic components involved in the commonly shared development of diabetes in obese individuals. A number of genetic studies have reported shared susceptibility loci between diabetes and obesity in humans. For example, a genome-wide association study revealed connections between type 2 diabetes and obesity-related metabolic diseases (or traits). This literature review aims to discuss the metabolic aspects of diabetes-obesity interactions from recent studies.

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by elevated blood glucose levels (Alkhatib, 2020; Muhammad *et al.*, 2013; van Dijk *et al.*, 2015). Type 2 diabetes has long been considered a disease of wealthier nations, yet it is now one of the world's leading public health challenges (Chandrasekaran and Weiskirchen, 2024). The prevalence of type 2 DM has increased in all parts of the world, with about 60% of cases currently occurring in developing countries (Ibrahim, 2022). The global diabetes epidemic is recognized as one of the greatest public health crises of the 21st century (Ismail *et al.*, 2021). An estimated 180 million people currently suffer from DM globally (Pinchevsky *et al.*, 2020). By 2030, this number is expected to rise to 366 million (Ibrahim, 2022). The global rise in diabetes incidence has been accompanied by an increase in obesity (Docherty and le Roux, 2020). Obesity is an independent risk factor for the development of type 2 DM (Kim and Scherer, 2021). The worldwide prevalence of obesity has nearly doubled since 1980: in 2014, 13% of the world's population was obese (Sohn *et al.*, 2020).

Many researchers have investigated the molecular mechanisms that interact between obesity and type 2 DM (Kim and Lee, 2021). Obesity-induced insulin resistance is the most commonly known association between obesity and type 2 DM (Tanase *et al.*, 2020). However, the relationship between obesity and type 2 DM is much more intricate than simply insulin resistance (Zatterale *et al.*, 2020). Type 2 DM is characterized by the loss of pancreatic β-cells, which causes impaired glucose-stimulated insulin secretion (Gupta *et al.*, 2020), leading to the development of hyperglycemia (Wu and Ballantyne, 2020). The pancreas, liver, and adipose tissues work together in a complicated feedback mechanism to maintain glucose homeostasis (Shim *et al.*, 2020). Pancreatic β-cells secrete insulin in response to elevated blood glucose levels, thus stimulating glucose uptake by the liver, muscle cells, and adipocytes while inhibiting glycogenolysis in the liver and lipolysis in adipocytes (Ababneh *et al.*, 2024; Amawi *et al.*, 2019; Ruze *et al.*, 2023). Insulin secretion is tightly regulated by glucose concentration and other hormonal signals (Alkhatib, 2024; Gordon *et al.*, 2021).

However, obesity and type 2 DM can cause detrimental alterations in this normally balanced feedback system (Tong *et al.*, 2022). These alterations include impaired insulin secretion from the pancreas, elevated hepatic glucose production, and peripheral insulin resistance. Simply stated, it is crucial to gain a deeper understanding of the molecular mechanisms linking obesity with type 2 DM (Chandrasekaran and Weiskirchen, 2024). The adoption of modern and digital technologies emphasizing innovative and integrative approaches in the healthcare system could serve as a driving force for improving public health (Alkhatib and Alabdulrazzaq, 2024; Iqbal, 2024; Iqbal and Ashraf, 2025; Iqbal *et al.*, 2021).

Genetic Factors in Diabetes and Obesity

The prevalence of obesity and type 2 diabetes (T2D) has increased rapidly worldwide, including low and middle-income countries where obesity and T2D prevalences are, in the majority of cases, higher in women than men (Herrera *et al.*, 2011). Obesity is a key risk factor for T2D and is characterized by abnormal or excessive fat accumulation that presents a risk to health (Karaderi *et al.*, 2015). Body mass index (BMI, weight (kg)/height (m)^2) is the most used parameter to define obesity, and for epidemiological and clinical studies, obesity is defined as BMI greater than or equal to 30 kg/m^2. Genetic, but also environmental, influences are key to the establishment of obesity and metabolic diseases, with evidence from familial aggregation, twin, and molecular studies (Scully *et al.*, 2021). Abdominal obesity and insulin resistance (IR) are main features of metabolic diseases and it has been shown that individuals of sub-Saharan African descent are more prone to store fat in subcutaneous depots and less prone to accumulation in visceral fat compared to white Caucasian individuals (Karaderi *et al.*, 2015). These physiological features are protective against IR and T2D, emphasizing that the same amount of adiposity

can lead to different health outcomes (Coker *et al.*, 2023; Dmour *et al.*, 2020).

The pandemic of obesity and T2D recently led the joint committee to define metabolic syndrome (MetS) as a complex disorder characterized by a cluster of risk factors for cardiovascular heart disorders including abdominal obesity, hypertension, dyslipidemia, and Insulin resistance (IR) (Alkhatib, 2021; Erekat *et al.*, 2014; Silveira Rossi *et al.*, 2022). The prescription of a low-intensity training exercise program as a preventive measure in MetS patients is effective in reducing body weight, body fat mass, and IR (Guembe *et al.*, 2020). Though the minimum effective dose of volume and intensity of exercise is largely debated, sedentary individuals are less prone to regulate energy intake in response to exercise training (Lemieux and Després, 2020). A bioenergetics and structural mathematical model was set-up to describe the perturbations in metabolic pathways caused by regular exercise intervention, showing the role of proton leak in the regulation of resting metabolic rate after endurance training and the relevance of a larger power back to basal in trained compared to sedentary subjects in the regulation of fat oxidation (Amawi and Alkhatib, 2020; Wutthi-In *et al.*, 2020).

Role of Insulin Signaling Pathway

Diabetes and obesity are two major health issues that have reached epidemic proportions worldwide, constituting a major socioeconomic burden with severe impacts on healthcare systems (Tong *et al.*, 2022). They strongly interact and increase the risk for numerous chronic diseases, such as cardiovascular diseases and cancers, and are tightly linked to metabolic syndrome (Martínez-Montoro *et al.*, 2022). Two major types of diabetes have been identified. Type 1 diabetes (T1D) is a monogenic autoimmune disease caused by the destruction of pancreatic β-cells by the immune system (Alkhatib, 2022; Szukiewicz, 2023). Type 2 diabetes (T2D) comprises around 90% of diabetes cases and is characterized by insulin resistance and the eventual failure of pancreatic β-cells. It is far more complex and involves genetic, epigenetic, and environmental factors (Feng *et al.*, 2020). Obesity is generally defined by a body mass index ≥ 30, but in terms of metabolic issues, it is more accurately defined by an excessive accumulation of fat, which can be metabolically active and harmful, especially abdominal fat (Ahmed and Mohammed, 2025; Organization, 2010). The concept of metabolically healthy obese subjects, although partially accurate, does not reduce the global risk of obese subjects (Milstein and Ferris, 2021). Nutritional habits, lack of household or outdoor activities, psychological factors, rare genetic diseases, and mutations in genes involved in the leptin-melanocortin pathway lead to extreme and syndromic forms of obesity. However, several homeostatic mechanisms help limit excessive weight gain, ranging from peripheral to central nervous control (Garg *et al.*, 2023). At the molecular level, obesity directly interferes with the insulin signaling pathway, notably in insulin-sensitive tissues such as muscle, liver, and adipose tissue (Martínez-Montoro *et al.*, 2022). Action Controller apparently contradictory effects of insulin on glucose homeostasis and lipid metabolism require the activation of distinct sets of genes, suggesting distinct repetitions (Yan, 2024).

Inflammation and Metabolic Dysfunction

Despite many years of research, the intricacies of diabetes and obesity are still not fully understood. In particular, the interactions between these two conditions remain poorly defined (Chen *et al.*, 2023; Molina-Montes *et al.*, 2021). Insight into the molecular aspects of energy homeostasis is crucial, as the incidence of obesity and type 2 diabetes is increasing globally, and the treatment of these metabolic disorders comes at significant social and economic costs (AlShuwayeb and Al-Khatib, 2013; Cao *et al.*, 2023). Understanding the mechanisms that underpin the connection between diabetes and obesity will facilitate the development of novel and more effective therapeutic strategies (Alkhatib, 2019; Liu *et al.*, 2020). Given that an unhealthy diet and sedentary lifestyles are important environmental contributors to these conditions, further insights will have critical implications for preventative

health care (Ma *et al.*, 2023). Unfortunately, the synergism between these metabolic diseases is more complex than the sum of the individual parts, and is in part poorly understood (Nielsen *et al.*, 2020). There is substantial evidence of a bidirectional causal relationship between type 2 diabetes and obesity, with insulin resistance lying at the heart of the condition (Targher *et al.*, 2021). In particular, the reduction of adipose tissue mass can improve glucose homeostasis and increase insulin sensitivity (Wang *et al.*, 2021).

Improving adipose tissue function may protect against insulin resistance. In general, metabolic homeostasis is regulated by a complex network of molecular signaling pathways (Wen *et al.*, 2022). As such, dysfunctional interaction between these signaling pathways can result in a range of metabolic diseases (Li *et al.*, 2022). Given that the interplay between obesity and type 2 diabetes is not a simple linear cause-and-effect pathway, this review will address the current state of understanding of the multifaceted molecular aspects of how the two conditions interact. Considering this complexity, it is important that future research fosters a multi-disciplinary approach (Zhao *et al.*, 2023). Protein interaction networks, as well as the integration of data across multiple biological scales, may be beneficial in further dissecting the molecular mechanisms that drive the interplay between diabetes and obesity (Kracht *et al.*, 2020).

Epigenetic Mechanisms in Diabetes and Obesity

Both obesity and diabetes arise from interactions between genetic and environmental factors (Gao *et al.*, 2021). Although the genetic basis of obesity and type 2 diabetes (T2D) is well established, there is rapidly growing evidence indicating that the pathogenesis of obesity and T2D is associated with diverse epigenetic dispositions (Kunysz *et al.*, 2021). Epigenetics refers to heritable changes in gene expression that occur without changes in the underlying DNA sequence (Ramos-Lopez *et al.*, 2021). There are four well-known epigenetic mechanisms: DNA methylation, histone modification, non-coding RNAs (ncRNAs), and chromatin organization (Gao *et al.*, 2021). Recent evidence indicates that epigenetic modifications linking environmental exposures to metabolic diseases, indicating that those born at low birth weights who have increased adiposity late in life have profound alterations in the epigenetic landscape of DNA in critical genes that are likely to mediate energy and lipid homeostasis (Ling *et al.*, 2022). What makes epigenetic marks attractive is their potential reversibility; they are amenable to nucleotide modifications in vivo catalyzed by a number of enzyme families (Singh *et al.*, 2020). This potentially affords a window on therapeutic interventions that might be triggered by alterations in lifestyle or chemical exposure aimed at the reversal or correction of epimutations (van Dijk *et al.*, 2015). It is proposed that environmental triggers may generate epigenetic marks that remain ‘locked’ after environmental challenge and may impinge or frame the response to metabolic triggering (Plunk and Richards, 2020). In the context of the study of metabolic diseases, there is an interest as to whether the epigenetic landscape of the exposed somatic tissues (epigenome) may be transmitted to the germline and affect next generation(s), hence increasing the risk for developing diabetes and other metabolic disorders (Mostafavi Abdolmaleky and Zhou, 2024). Studies from animal and human population-based cohorts have shown that pre-conceptional and gestational exposures to macronutrients can indeed lead to the setting of the epigenome in the germline and affect the metabolic and reproductive health of the progeny in sexually dimorphic characteristics (Dalfrà *et al.*, 2020).

CONCLUSION

Type-2 diabetes (T2D) and obesity are multifaceted diseases influenced by the interplay of genetic makeup, the environment, and poorly defined triggering elements. Hence, the propensity to develop them is not always shared but is disorder-dependent as well. Research effort is increasingly developing from both views

to unveil a complete understanding on how T2D and obesity crosstalk and species-specific complex molecular mechanisms. Practically all the organs and tissues in the body are involved in the control of food intake, nutrient absorption and maintenance of metabolic homeostasis. Given such a redundancy and mere at the edge of current understanding or even technically accessible ways, the attention is shifted to non-linear approaches to this issue. Several paradigmatic topics taking part in these extremely intricate molecular strategies are highlighted. Though obesity is recognized as a major contributor to T2D due to lipid-sustained molecular interference with the complete insulin signal transduction path, increasing evidence is present supporting the opinion that hyperglycemia-induced oxidative stress is also relevant. Anti-inflammatory drugs or anti-adipogenic therapies are proof that other links are unveiled and pave the way for future investigation of crosstalk.

CONFLICT OF INTEREST

The author hereby declares no conflict of interest.

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