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Type 2 Diabetes and Obesity: A Comprehensive Review

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ABSTRACT

Type 2 diabetes mellitus (T2DM) and obesity are closely interrelated metabolic disorders that together represent a growing global health burden. Obesity is a major risk factor for T2DM and plays a central role in its pathogenesis through mechanisms involving insulin resistance, dysregulated lipid metabolism, chronic low-grade inflammation, and altered adipokine secretion. Modern lifestyles characterized by physical inactivity and excessive caloric intake have created environmental conditions that interact with genetic predisposition to promote both obesity and diabetes. This review critically examines the relationship between obesity and T2DM, with particular emphasis on the role of free fatty acids, visceral adiposity, adipocytokines, and insulin resistance. In addition, patterns of genetic investigation relevant to obesity and T2DM are discussed, highlighting the importance of studying quantitative traits and early-life phenotypes. Understanding these interconnections is essential for the development of effective preventive and therapeutic strategies for both conditions.

Keywords: Type 2 diabetes mellitus; Obesity; Insulin resistance; free fatty acids; Adipocytokines

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Introduction

Diabetes mellitus and obesity exhibit a complex and bidirectional relationship, with type 2 diabetes mellitus being strongly associated with excess body fat accumulation [1]. Obesity is widely recognized as one of the most important risk factors for the development of T2DM, primarily through the induction of insulin resistance [2,3]. Nevertheless, the occurrence of T2DM in lean individuals, including those with latent autoimmune diabetes in adults (LADA), indicates that obesity is not the sole determinant of disease development [4]. The strength and nature of the association between obesity and T2DM appear to vary according to the type of obesity and underlying metabolic characteristics [4]. The etiology of obesity itself is multifactorial and heterogeneous. Genetic predisposition plays a significant role, interacting with environmental and lifestyle factors such as diet, physical activity, and socioeconomic conditions [5–7]. Understanding the mechanisms linking obesity and T2DM is essential, as reduction of excess body weight remains a cornerstone in both the prevention and treatment of T2DM worldwide [6-9].

Free Fatty Acids and Triglycerides in the Development of Type 2 Diabetes Mellitus

Free fatty acids (FFAs) serve as a major energy source for organs such as the liver, skeletal muscle, and kidneys and are key substrates for hepatic triglyceride synthesis. During prolonged fasting, FFAs provide an alternative energy source to glucose, thereby preserving glucose availability for the brain and reducing protein catabolism. FFAs are stored predominantly as triglycerides within white adipose tissue and are released through hormonally regulated lipolysis [10]. Insulin is the most potent antilipolytic hormone and plays a central role in suppressing FFA release from adipocytes [11]. In states of insulin resistance, adipocytes become less responsive to insulin, resulting in elevated circulating FFA levels [12,13]. Increased plasma FFA concentrations are a characteristic feature of T2DM [5,6] and are strongly implicated in the development of both insulin resistance and pancreatic β-cell dysfunction. Consequently, lowering FFA levels has emerged as an important therapeutic objective in the management of T2DM. Prospective epidemiological studies have demonstrated that elevated FFA concentrations predict long-term deterioration of glucose tolerance and progression to T2DM [7]. In addition, high FFA levels are associated with independent risk factors for cardiovascular disease, including hypertension and endothelial dysfunction [1–3,8,14]. These findings underscore the importance of dyslipidaemia management alongside glycaemic and blood pressure control in patients with T2DM.

Obesity, Insulin Resistance, and Pathogenic Hypotheses

Insulin resistance may originate, at least in part, within adipose tissue [15]. Two complementary hypotheses have been proposed to explain how obesity induces insulin resistance [16].

The Adipokine and Inflammation Hypothesis

Obesity alters the profile of hormones secreted by adipose tissue, collectively referred to as adipokines. In obese individuals, adipose tissue secretes higher levels of adipokines that impair insulin sensitivity and lower levels of those that enhance insulin action. Obesity is associated with increased secretion of chemokines from adipocytes, leading to macrophage infiltration and activation within adipose tissue [17]. Activated macrophages release pro-inflammatory cytokines that interfere with insulin signaling pathways and contribute to systemic insulin resistance.

Interplay Between Central Obesity and Free Fatty Acids

Central obesity, characterized by excess fat accumulation in visceral and upper-body subcutaneous depots, is most strongly associated with metabolic and cardiovascular complications [18–20]. Visceral adipose tissue exhibits increased lipolytic activity, resulting in enhanced FFA flux into the portal circulation [21]. Elevated portal FFA levels contribute to hepatic insulin resistance, hyperinsulinemia, and increased hepatic glucose production (Figure 1). Additionally, increased peripheral FFA levels may impair insulin-stimulated glucose uptake in skeletal muscle and negatively affect pancreatic insulin secretion [10].

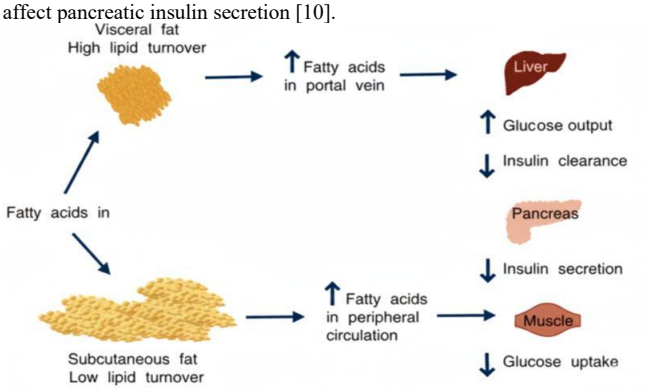

Figure 1: Free fatty acid turnover in visceral and subcutaneous adipose tissue

Visceral Obesity and Adipocytokines

Both visceral and subcutaneous adipose tissues secrete a wide range of bioactive molecules known as adipocytokines. These include adipose tissue–specific factors such as leptin and adiponectin, as well as non-specific cytokines such as plasminogen activator inhibitor-1, tumor necrosis factor-α, and interleukins [22]. Adipocytokines play key roles in the regulation of glucose and lipid metabolism, oxidative stress, and vascular homeostasis. Leptin, IL-6, and TNF-α are known to promote insulin resistance, whereas adiponectin enhances insulin sensitivity. Elevated circulating leptin levels have been identified as predictors of metabolic syndrome, particularly hypertension and impaired fasting glucose [23].

Visceral Obesity and Insulin Resistance

Visceral adiposity contributes to insulin resistance through increased production of inflammatory cytokines, including IL-6, TNF-α, transforming growth factor-β1, and monocyte chemoattractant protein-1, primarily by adipose tissue–resident macrophages (Figure 2) [24]. These inflammatory

pathways also contribute to increased cardiovascular risk independently of insulin resistance.

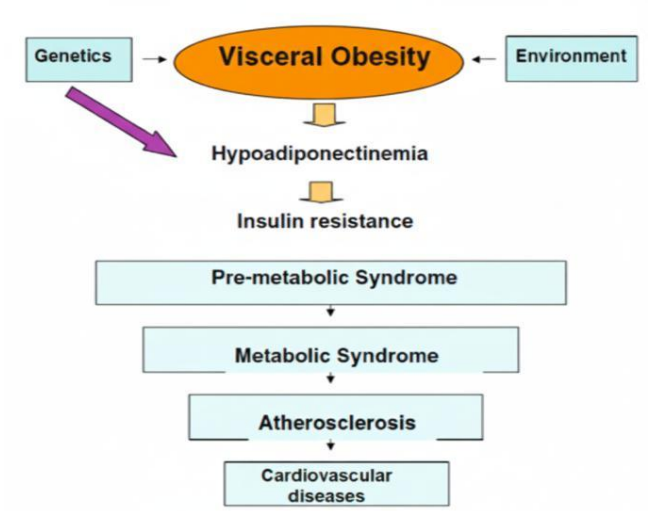

Figure 2: Role of visceral obesity in the pathogenesis of metabolic syndrome

Visceral obesity is also associated with endothelial dysfunction, hypercoagulability, oxidative stress, and reduced nitric oxide bioavailability [25–28]. Genetic factors further modulate susceptibility to insulin resistance, while hyperinsulinaemia and visceral fat accumulation contribute to the development of arterial hypertension through sympathetic nervous system activation [29–32].

Biological Effects of Adiponectin in Humans

Adiponectin is a unique adipokine whose expression decreases with increasing adiposity [33,34]. Visceral fat accumulation may suppress adiponectin synthesis through inhibitory mediators such as TNF-α [35,36]. Plasma adiponectin levels are higher in women and lean individuals and are inversely associated with insulin resistance, hypertriglyceridaemia, hypertension, and T2DM [37–39]. Clinical studies have demonstrated potential anti-atherogenic effects of adiponectin, with higher circulating levels associated with reduced risk of myocardial infarction in some populations [40]. However, other prospective studies have failed to confirm a consistent cardioprotective effect, suggesting population-specific differences in adiponectin action [41,42].

Adiponectin, Obesity, and Insulin Resistance

Experimental studies using adiponectin-deficient animal models and recombinant adiponectin administration have demonstrated beneficial effects on body weight regulation and insulin sensitivity in liver and muscle [37]. In humans, low adiponectin levels predict the development of T2DM but do not necessarily predict obesity onset. Importantly, weight reduction has been shown to increase plasma adiponectin concentrations and improve insulin sensitivity [43].

Genetic Investigation of Obesity and Type 2 Diabetes Mellitus

The genetic basis of obesity and T2DM is complex and involves multiple genes with small individual effects interacting with environmental factors. Quantitative genetic approaches focus on measurable traits rather than categorical disease definitions [44]. Obesity-related traits may include anthropometric measurements, body composition parameters, and biochemical markers such as leptin, insulin, and FFA levels. These traits represent intermediate phenotypes linking genetic variation to overt disease manifestations (Figure 3). However, distinguishing causal mechanisms from disease consequences remains challenging, as many traits contribute to both [44].

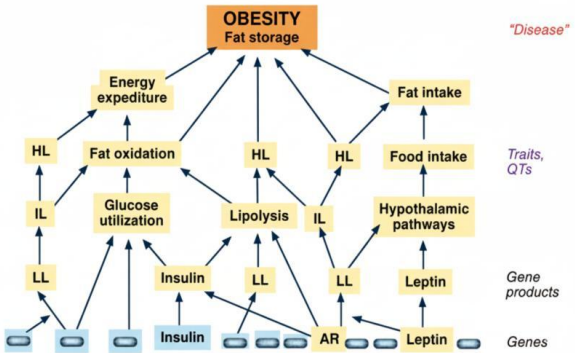

Figure 3: Relationship between genes, intermediate phenotypes, and obesity-related traits

Studying Early-Life Traits in Obesity and Diabetes Genetics

Genetic studies of complex metabolic diseases are particularly informative when conducted in children and adolescents [44]. Early-life phenotypes may better reflect evolutionary adaptations related to energy storage, insulin sensitivity, and glucose allocation to the brain [45,46]. Studying young individuals also facilitates long-term follow-up, predictive genetic epidemiology, and family-based analyses, including sibling pair and transmission disequilibrium studies [47].

Conclusion

Visceral obesity plays a pivotal role in the development of T2DM by increasing free fatty acid mobilization and promoting chronic inflammation, thereby inducing insulin resistance. Adipocytokines, particularly adiponectin, represent important molecular links between adiposity and metabolic dysfunction. Genetic predisposition further modulates susceptibility to obesity-related insulin resistance and diabetes. A systematic approach focusing on pathogenic traits measured early in life may enhance understanding of the genetic and molecular mechanisms underlying obesity and T2DM. Continued research across diverse populations is essential to develop effective prevention and treatment strategies for these interrelated conditions.

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