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Role of Weight Loss in Type-2 Diabetes Remission

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Abstract

Obesity is the most significant risk factor for developing and progressing type-2 diabetes, with the risk of increasing linearly alongside BMI (Body Mass Index), across all age groups according to the International Diabetes Federation (IDF). Its pandemic-level prevalence makes treating obesity and weight loss crucial for preventing and managing type-2 diabetes worldwide. The cellular and physiological mechanisms linking obesity to type-2 diabetes are complex, involving adiposity-induced changes in β-cell function, adipose tissue biology, and multi-organ insulin resistance. These effects can often be normalized with adequate weight loss. Clinical studies show that moderate, sustained weight loss improves blood glucose levels, insulin action, and reduces the need for type-2 diabetic medications. A combined approach of diet, exercise, and lifestyle modifications effectively reduces obesity and mitigates the complications of diabetes. This strategy also aids in the prevention, control and remission of type-2 diabetes.

Keywords: Obesity; Type-2 Diabetes; Pathophysiology; Prevalence; Adipose Tissue; Hepatic Glucose; Insulin Resistance; Insulin Sensitivity; Therapeutic Approach

Abbreviations: IDF: International Diabetes Federation; FFAs: Free Fatty Acids; NCDs: Non-Communicable Diseases; NAFLD: Non-Alcoholic Fatty Liver Disease; BMI: Body Mass Index; IGT: Impaired Glucose Tolerance; IFG: Impaired Fasting Glucose; ECM: Extracellular Matrix; IDF: International Diabetes Federation; GWAS: Genome-Wide Association Study.

Introduction

The rapid development of global urbanization and modernization has lasting effects on lifestyle aspects such as unhealthy eating behaviours, lack of exercise, increased stress and environmental factors. These factors contribute to the alarming growth of obesity and type-2 diabetes worldwide. According to the WHO [1], at least 2.8 million people die every year from being overweight or obese. Interestingly, one-third of the world's population is classified as either overweight or obese using BMI as a measure. On the other hand, diabetes is a global issue; it does not respect borders or social class. The association between obesity and type-2 diabetes has been recognized for decades.

Inspired by their connected epidemiology and numerous clinical findings [2], researchers have extensively explored the deeper correlations between the pathogeneses of these two common metabolic disorders, obesity and type-2 diabetes.

In this literature review, we will provide information on the clinical definition of obesity and Type-2 diabetes, on the adipose tissue biology, and on mechanisms responsible

for the link between excess adiposity and type-2 diabetes and the effects of weight (fat) loss as therapeutic metabolic condition.

Obesity and Insulin Resistance

Adipose Tissue Biology: Adipose tissue is the body's main fuel reserve, offering a crucial energy source during food scarcity. Triglycerides are hydrophobic and highly energy-dense, making them a five-fold better fuel per unit mass than glycogen. They are compactly stored as an oil inside adipocytes and produce ~9.3 kcal per gram when oxidized, whereas glycogen is stored intracellularly as a gel (containing water) and produces only 4.1 kcal per gram when oxidized [3]. Adipose tissue must be metabolically flexible to cope with large and rapid changes in energy balance during feeding and fasting and to adjust to long-term changes that cause adipose tissue expansion or reduction. An increase in adipose tissue mass after chronic positive energy balance is due to accumulation of triglycerides in adipocytes, which enlarges their mass and requires structural remodelling to support the expanded adipocyte mass [4]. The adaptive responses of adipose tissue to its expansion are crucial for adipose tissue health and systemic metabolic homeostasis, and differences in these responses likely contributing to the metabolic health heterogeneity in people with obesity [5,6].

Adipose tissue also produces and secretes adipokines and exosomes, which are involved in the regulation of important physiological functions, such as appetite, reproductive function and insulin action [7].

Studies demonstrate that obesity-induced alterations in adipose tissue metabolism, extracellular matrix formation, immune cells (primarily macrophages) and inflammation (adipose tissue macrophages encoded by SERPINE1) are involved in regulating metabolic function in other organs. It must somehow communicate with these organs. Several potential signaling mechanisms have been proposed that involve the secretion of adipose tissue products into the circulation that are then delivered to target tissues. These products include proinflammatory proteins, adiponectin, FFAs (Free Fatty Acids) and exosomes, which are shown in Figure 1. Differences in these factors among individuals likely contribute to the heterogeneity in metabolic health associated with obesity in people [1].

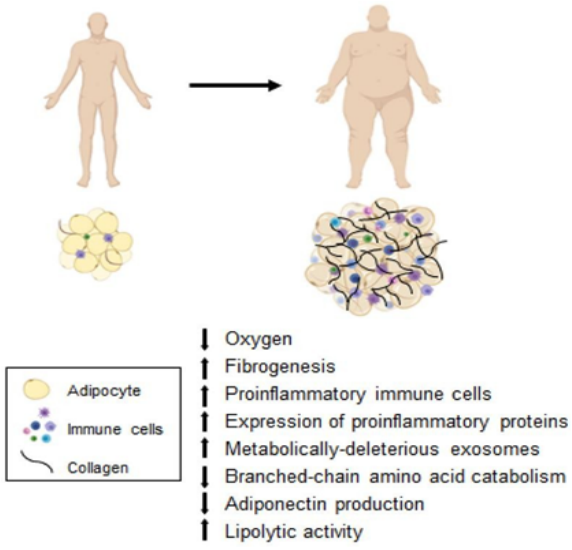

Figure 1: Alterations in adipose tissue biology associated with metabolic dysfunction in persons with obesity.

Why obesity is involved in diabetes type2: In the last two decades, obesity has become a global pandemic, affecting nearly every organ system and emerging as a severe public health problem and one of the most common non-communicable diseases (NCDs) [8].

Obesity is defined as the excessive accumulation of fat in the body, either in specific organs known as ectopic fat, or throughout the body. Obesity is recognized as a chronic, relapsing and multifactorial disease determined by genetics, biology, healthcare access, mental status, sociocultural and socioeconomic factors, personal lifestyle, and other environmental triggers. It threatens nearly every organ system and is associated with metabolic disorders and co-morbidities such as type-2 diabetes, cardio- and cerebrovascular diseases, and cancers, affecting both physical and mental health. One of the main causes of obesity is an imbalance between excess energy stored and

the energy utilized by the body, which can disrupt nutrient signals leading to insufficient energy expenditure [9]; (World Obesity Federation).

The diagnosis of obesity relies on BMI cut-off and the relationship between body weight, fat distribution pattern and visceral fat. Since BMI alone is insufficient to evaluate obesity, as it is a diverse condition, Table 1 shows the classification of obesity based on BMI and waist circumference [10].

Condition	BMI (kg/m^2)	Disease Risk Relative to Normal Weight and Waist Circumference
		Men ≤ 40 inches (≤102 cm) Women ≤ 35 inches (≤88 cm)
Normal	18.5–24.9	Data
Overweight	25.0–29.9	Increased
Obese	30.0–34.9 (class 1)	High
	35.0–39.9 (class 2)	Very high
Extremely Obese	≥40	Extremely high

Table 1: Classification of obesity based on body mass index and waist circumferences.

Interestingly, by 2030, nearly 14% of men and 20% of women worldwide (over 1 billion people) are expected to suffer from obesity. The percentages of adults with obesity (BMI ≥30 kg/m^2), severe obesity (BMI ≥35 kg/m^2), and extreme obesity (BMI ≥40 kg/m^2) are projected to be 18%, 6%, and 2%, respectively.

Obese individuals develop insulin resistance, which is characterized by impaired insulin action in the liver and reduced glucose uptake in fat and muscle. Excessive body fat accumulation leads to various metabolic abnormalities and diseases, including insulin resistance, atherogenic dyslipidemia (high triglycerides and low HDL cholesterol), nonalcoholic fatty liver disease (NAFLD), β-cell dysfunction, prediabetes and type-2 diabetes.

In obese individuals, non-esterified fatty acids play a crucial role in the development of insulin resistance and beta cell dysfunction [1].

In general, a progressive increase in body mass index (BMI), which provides an index of adiposity, is associated with a progressive increase in the risk of developing type-2 diabetes [11]. However, the distribution of fat and triglyceride modifies the risk of adiposity-induced metabolic dysfunction [3]. People who are obese with a predominant increase in upper body fat (abdominal subcutaneous and intra-abdominal fat), intrahepatic triglyceride content, intramyocelluar lipid content and pancreatic fat, are at higher risk of developing type-2 diabetes than those with a lower body (gluteofemoral) fat phenotype. In fact, increased gluteofemoral body fat mass is associated with decreased plasma triglyceride and increased HDL-cholesterol concentrations, decreased fasting blood glucose and insulin concentrations, increased oral glucose tolerance and insulin sensitivity, and decreased risk of type-2 diabetes in people who are lean, overweight or obese [12].

Type-2 Diabetes

What is Type-2 Diabetes: Diabetes is a chronic metabolic disorder with multiple causes, characterized by consistently high blood glucose levels due to defects in insulin secretion, action or both. Type-2 diabetes is more common than type 1 diabetes, accounting for 90–95% cases. It is strongly influenced by genetics and involves resistance to insulin action and inadequate compensatory insulin secretion [13].

The diagnosis of Type-2 diabetes is made when the patient meets one of the following criteria: glycated hemoglobin (HbA1C) ≥ 6.5%, fasting blood glucose ≥ 126 mg/dL or 2-hours postprandial glucose ≥ 200 mg/dL. Diabetes-related morbidity and complications can be substantially reduced with tight glycemic control, aiming for an HbA1c of less than 7% [14].

The global rise in obesity is inevitably contributing to the increasing prevalence of type-2 diabetes, which is a chronic disease occurs when the body fails to produce enough (or any) insulin or cannot effectively use the insulin it produced, leading to elevated blood glucose (hyperglycemia) as a primary manifestation [15].

Most patients with type-2 diabetes are obese, with a higher percentage or abnormal distribution of body fat, which is related to the pathophysiology of Type-2 diabetes. Adipose tissue promotes insulin resistance by releasing more free fatty acids.

Other contributing factors include peripheral insulin resistance, dysregulation of hepatic glucose production, decreased β-cell function and β-cell failure [1].

Being strongly linked to overweight and obesity, aging, ethnicity, and family history, Type-2 diabetes, accounts for over 90% of diabetes cases worldwide, fuelled by relative insulin deficiency owing to pancreatic β-cell dysfunction and insulin resistance [16].

Type-2 diabetes is preventable and manageable through education, support, lifestyle changes, required medication, and other available treatments, with growing evidence suggesting the possibility of mitigation. However, due to the uncertainty of the exact time of the onset and distinct duration of the prediabetic period, nearly 30-50% of patients remain undiagnosed until complications arise and thus treatments are required. Beyond those currently diagnosed, so many people are at high risk of developing Type-2 diabetes due to impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) although the later onset of T2DM is likely to be preventable. In 2021, 541 million adults were estimated to have IGT and 319 million to have IFG, and these numbers projected to rise to 730 million and 441 million by 2045 [15].

Hepatic Glucose, Insulin and Lipid Metabolism: The liver is the main source of endogenous glucose production, with about 80% derived from hepatic glycogenolysis (glucose produced from the breakdown of liver glycogen) and gluconeogenesis (glucose produced from precursors such as lactate, glycerol and amino acids), and about 20% from gluconeogenesis by the kidneys [17].

In lean individuals, glycogenolysis and gluconeogenesis contribute equally to total endogenous glucose production, but gluconeogenesis is higher in those with obesity or type-2 diabetes [18].

An increase in gluconeogenesis causes fasting hyperglycemia, and impaired suppression of endogenous glucose production and gluconeogenesis after meal ingestion leads to postprandial hyperglycemia in prediabetes and type-2 diabetes [19].

Pancreatic β-cells secrete insulin directly into the portal vein for delivery to the liver, which is the major site for insulin clearance. Plasma insulin concentration is determined by the balance between the rate of insulin secretion and the rate of insulin removal by the liver and extrahepatic tissues. Insulin in the portal vein is the major regulator of hepatic glucose production. People with obesity typically have impairment in the ability of insulin to suppress hepatic glucose production [20].

However, increased hepatic glucose production occurs when the increased secretion of insulin is not adequate to compensate for insulin resistance as in people with impaired fasting glucose or when the secretion of insulin decreases as in people with type-2 diabetes [21].

Insulin resistance in adipose tissue has indirect effects on hepatic glucose metabolism because impaired suppression of adipose tissue lipolysis increases the release of fatty acids that are delivered to the liver, which increases hepatic gluconeogenesis [22].

The Mechanism Linking Obesity and Type-2 Diabetes

Inspired by their connected epidemiology and plenty of clinical findings, researchers have made considerable efforts to investigate the deeper correlations between the pathogeneses of these two common metabolic disorders [2].

The close relationship between obesity and diabetes has led to the term “diabesity”, which highlights that the majority of individuals with diabetes are obese or overweight [15].

While type-2 diabetes is influenced by genetic predisposition and ethnicity which are non-modifiable risk factors, it can still be prevented or managed by addressing modifiable risk factors such as obesity. Despite recent advancement in management strategies, obesity and diabetes remain a significant interconnected public health challenge worldwide.

However, Type-2 diabetes can also occur inversely before obesity in some individuals with inherent insulin resistance resulting in increased hepatic glucose production and elevated insulin levels, which are the actual cause of obesity. This rare and challenging concept beyond the scope of this article is reviewed elsewhere [23].

Below, we will explore the mechanistic link between obesity and diabetes. The first to mention is the overlaps in their genetics/epigenetics revealed by the Genome-Wide Association Study (GWAS) [24].

Once obesogenic and diabetogenic environmental factors amplify the genetic susceptibilities, the ectopic expansion of adipose tissue and excessive accumulation of certain nutrients and metabolites sabotage the metabolic balance via insulin resistance, dysfunctional autophagy, and microbiome-gut-brain axis, which further exacerbate the dysregulation of immunometabolism through systemic inflammation leading to an accelerated loss of β-cell function and gradual elevation of blood glucose [25].

Genetics and environment factors: The pathogenesis of Type-2 diabetes is characterized by the inflammatory component inducing progressive loss of β-cell insulin secretion with co-existing insulin resistance [14,26],

impacting early β-cell function and cell fate [27], where overweight and obesity are deemed the most effective "accelerator" (Figure 2).

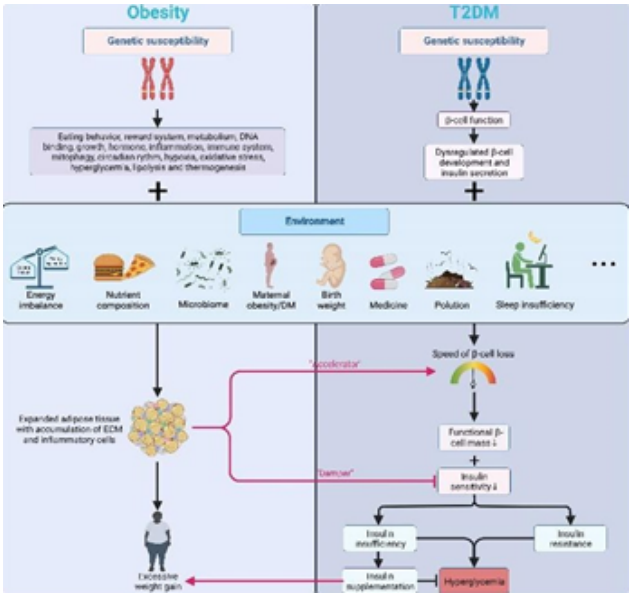

Figure 2: Genetic and environmental factors affecting islet function and connecting obesity and Type-2 diabetes. Genetic factors mainly alter the energy balance in obesity while regulating the development and function of β-cells in Type-2 diabetes. Being further promoted by various environmental factors, obesity accelerates the β-cell loss and blunts insulin signaling in Type-2 diabetes. Meanwhile, insulin prescribed to patients with Type-2 diabetes can have a weight-increasing effect. Arrows in color indicate the interactions between obesity and Type-2 diabetes. (ECM, extracellular matrix) [28].

Many patients with obesity can go through a transitional stage called "Prediabetes" before eventually developing hyperglycemia, which refers to the scenario when the glucose levels are not high enough for a Type-2 diabetes diagnosis while the normal carbohydrate metabolism is compromised [13].

Prediabetes has a solid link to obesity (particularly abdominal or visceral obesity), hyperlipidemia, and hypertension. In patients with Type-2 diabetes, genetic signals mainly regulate β-cell development and function [27,29] (Figure 2).

Environmental factors and hyperglycemia contribute to epigenetic changes in DNA and histones, modulating gene expression in organs implicated in the pathogenesis and progression of Type-2 diabetes and β-cell function.

Higher maternal BMI before pregnancy, greater calorie intake, more significant gestational weight gain, and maternal hyperglycemia are closely related to childhood obesity and Type-2 diabetes. More importantly, maternal hyperglycemia and gestational diabetes are associated with precursors of Type-2 diabetes (e.g., insulin resistance) in offspring, further indicating a powerful effect of maternal hyperglycemia on pancreatic β-cell development and function. Later in adulthood, the aging-associated decline in the β-cell responsiveness to carbohydrates partly explains the growing glucose intolerance with aging.

Microenvironmental Remodelling Related to Adiposity Ectopic Expansion of Adipose Tissue: Obesity is characterized by the overaccumulation of adipose tissue. three types of adipocytes have been identified in the human body [30].

The aberrant accumulation and expansion of adipose tissue in non-adipose sites in obesity elevates the levels of certain metabolites, with the overproduction of inflammatory cytokines fuelling systemic inflammation and disruption of cellular function, jointly contributing to impaired insulin signaling, damaged physiological and metabolic regulation, locally induced loss of β-cell function, the onset of hyperglycemia, and the eventual occurrence of Type-2 diabetes [28].

Nutrients and Metabolites: The contribution of obesity to insulin resistance is beyond the impairment of insulin signaling but involves the interplays of various metabolic pathways and essential nutrients and metabolites. Some nutrients and metabolites can directly impact insulin signaling by regulating the components of the insulin signaling pathway or indirectly mediate the substrates flux of metabolic pathways such as lipogenesis, lipid oxidation, protein synthesis, degradation, hepatic gluconeogenesis, and the post-translational modulation of proteins.

Autophagy: Autophagy maintains cellular quality and organ function as a key but conserved homeostatic process via the disposal and recycling of cellular components while eliminating hazardous cells containing potentially toxic proteins, lipids, and organelles.

Alterations of autophagy in different metabolic organs during the transition from overnutrition and obesity to Type-2 diabetes. The excessive intake of nutrients such as lipids, glucose, and amino acids results in the suppression of autophagy via different signaling pathways and contributes to obesogenesis by increasing the accumulation of lipids, and proteins, enhancing low-grade systemic inflammation and exacerbating insulin signaling [28].

The (Microbiome-Gut-Brain) Axis: Regulated by various

factors, the microbiome-gut-brain axis is one of the most critical mechanisms regulating whole-body metabolism, adiposity, energy balance, and central appetite and food reward signaling in humans (Figure 3). The aberrance of this axis is closely associated with several metabolic diseases, including obesity and Type-2 diabetes [31].

Significantly, microbiome dysfunction is the main culprit responsible for energy imbalance, fat deposition, inflammation, insulin resistance, glucolipotoxicity, and dysregulation of endocrine signaling pathways by either direct or indirect effect [32].

In general, the high diversity of the microbiome is crucial in maintaining a healthy physical condition. The composition of the microbiome is both endogenously and exogenously shaped by multiple factors, including maternal environment, age, ethnicity, diet, medication (especially antibiotics), and genetics, among which the diet is predominately determinative, and the composition of gut microbiome changes with the development of obesity and Type-2 diabetes [33].

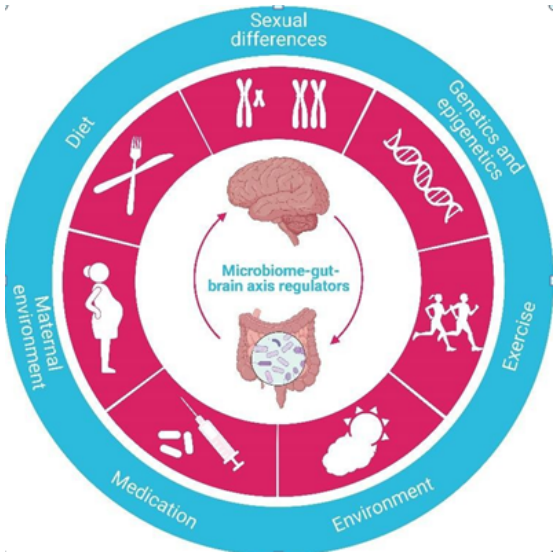

Figure 3: Regulators of the microbiome-gut-brain axis. The crucial function of the microbiome-gut-brain axis is regulated by various factors, such as diet, sexual differences, genetics/epigenetics, exercise, environment, medication, and maternal environment [28].

Discussion

Management and Treatment of Type-2 Diabetes

Mutual Effect of Available Treatment for Obesity and Type-2 Diabetes: Type-2 diabetes is a slowly progressing metabolic disease closely related to obesity. Hence, obesity management ameliorates or even remits the Type-2 diabetes in many patients. Likewise, since nearly 2/3 of the patients with Type-2 diabetes have a weight problem [34], some anti-diabetic treatments (such as oral medications) can also reduce body weight. In general, treatments effective for both obesity and Type-2 diabetes include lifestyle interventions (such as dietary modification, physical activity, and behavioral therapies), pharmacotherapy, medical devices, and bariatric surgery.

Effects of Weight (Fat) Loss: Weight loss can have profound therapeutic effects on metabolic function, type-2 diabetes and diabetes comorbidities [35] (Figure 4). Moderate 5%-10% weight loss improves glycemic control, plasma triglyceride and HDL-cholesterol concentrations and blood pressure. Greater weight loss can achieve diabetes remission, but the rate of remission depends primarily on the duration of diabetes, the ability of weight loss to improve β-cell function, and the criteria used to define remission [36].

In contrast to weight (fat) loss achieved by negative energy balance induced by bariatric surgery, diet therapy, or pharmacotherapy, surgical removal of adipose tissue does not result in metabolic benefits [37].

Weight loss has potent effects on insulin action and even 5% weight loss improves multiorgan (adipose tissue, liver and skeletal muscle) insulin sensitivity [38].

The sensitivity of adipose tissue and the liver to small decreases in body weight suggest the therapeutic effects of weight loss are mediated, at least in part, by alterations in adipose tissue and liver physiology and the effect of adipose tissue on systemic signaling mechanisms, such as adiponectin, PAI-1 and exosomes released from adipose tissue [39,40].

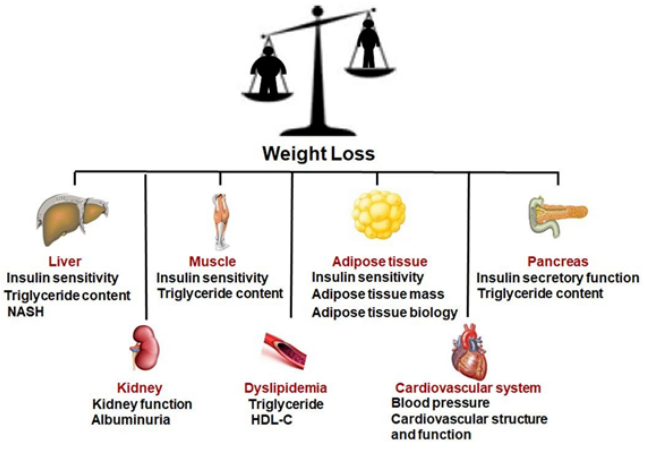

Figure 4: Multi-organ therapeutic effects of weight loss [1].

Conclusion

Obesity, especially with increased abdominal fat and intra-abdominal fat distribution and increased intrahepatic and intramuscular triglycerides, is a major risk factor for prediabetes and type-2 diabetes due to insulin resistance and β-cell dysfunction. The rise in global obesity prevalence has led to a similar increase in type-2 diabetes. Accordingly, the worldwide increase in the prevalence of obesity has led to the concomitant increase in the prevalence of type-2 diabetes.

Understanding the mechanisms linking excess body fat to type-2 diabetes can lead to new therapeutic interventions and treat this weakening disease.

Reducing body fat mass through negative energy balance, not by surgical removal, can improve or normalize obesity-induced metabolic dysfunction and potentially achieve diabetes remission if β-cell function is well restored.

Type-2 diabetes is preventable and manageable through education, support, lifestyle changes, required medication, and other available treatments, with growing evidence suggesting the possibility of mitigation.

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