

Investigating the Pathogenesis and Treatment of Type 2 Diabetes from the Perspective of Adipose Tissue

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Abstract: Type 2 diabetes mellitus (T2DM) has a high prevalence worldwide; its cardiac, renal, and visual complications greatly affect patients' quality of life. This, together with the large patient base, makes clinical health management of T2DM a problem. Existing studies have shown that obesity and the onset of T2DM are highly correlated, which can start from the earliest lipid metabolism problems and ultimately develop into T2DM. Moreover, adipose tissue can also seriously affect patient treatment by affecting insulin secretion, promoting pancreatic β -cell proliferation, and increasing insulin resistance. Our study describes the association between obesity and T2DM, summarizes the role played by the adipose tissue in T2DM, and focuses on fatty acid esters of hydroxy fatty acids (FAHFA), whose role in improving insulin secretion and increasing insulin sensitivity shows greater potential in T2DM. In addition, we summarize the existing more mature clinical treatment strategies, such as life interventions, drugs, and surgery, which can help control blood glucose levels and reduce adipose-related insulin resistance by reducing the adipose tissue. Among these treatments, Chinese medicine is another factor worth exploring. However, due to the influence of geography, culture, and other factors, this method has only achieved some success in China and part of the East Asia region and has been applied clinically. Although there is no evidence of clinical benefit for obesity or adipose tissue, its clinical benefit for T2DM has been demonstrated; therefore, there is still a need to develop it, as well as considerable potential for development.

Keywords: T2DM, obesity, adipose tissue, FAHFA, treatment, Chinese medicine

Introduction

The prevalence of diabetes mellitus (DM) is rapidly increasing owing to changes in diet and lifestyle.¹ Concurrently, the incidence of type 2 diabetes mellitus (T2DM) is increasing among individuals aged < 40 years.² Current statistics indicate that approximately 537 million people worldwide live with diabetes, with over 90% diagnosed with T2DM.³ Projections suggest that this number could increase to 783 million by 2045.⁴ Genome-wide association studies have highlighted that the genetic variants linked to T2DM predominantly affect islet function, with single gene mutations contributing minimally, accounting for less than 20% of the overall disease risk.⁵ T2DM encompasses more than just persistent elevations in blood glucose levels; it is a complex cardiorenal-metabolic disease driven by a chronic positive energy balance.⁶ Diabetes continues to be the leading cause of blindness, kidney failure, heart attack, stroke, and lower limb amputations globally.⁷

Obesity and diabetes are interrelated diseases with several key pathogenic mechanisms.⁸ Obesity is a significant contributor to insulin resistance and plays a role in promoting β -cell failure.⁹ Although not all patients with T2DM are obese, most exhibit adipose tissue pathology.¹⁰ Conversely, weight loss can reduce abnormal adipose tissue, improve the metabolic status,¹¹ and even lead to the remission of T2DM in some individuals.¹²

The World Health Organization (WHO) characterizes obesity as a chronic complex disease characterized by excessive fat accumulation that can lead to significant health complications. This condition increases the risk of T2DM and cardiovascular disease, adversely affects bone health and reproductive function, and increases the risk of certain cancers. Furthermore, obesity exhibits geographical diversity with prevalence rates ranging from 31% to 67% in Southeast Asia, Africa, and the Americas.¹³ According to WHO data, in 2019, excess body mass index (BMI) was responsible for approximately 5 million deaths from noncommunicable diseases, including cardiovascular disease, diabetes, cancer, neurological disorders, chronic respiratory diseases, and digestive diseases. The American Association for Clinical Endocrinology similarly defines obesity as an obesity-induced chronic disease, also referred to as an adiposity-based chronic disease.¹⁴ Importantly, it emphasizes the necessity of lifestyle modifications and treating overweight and obesity as essential components of prediabetes and diabetes management.

Physiological Functions of Adipose Tissue

Adipose tissue is the largest endocrine and immune organ; it is characterized by significant heterogeneity and plasticity.¹⁵ Numerous studies have demonstrated that adipose tissue plays a vital role in systemic metabolic regulation and energy homeostasis.¹⁶ It can be classified into three types: white, brown, and pink adipose tissue. Brown adipose tissue can be further divided into classic and inducible brown adipose tissue (also known as beige adipose tissue).

Another classification approach is based on the anatomical location, distinguishing between subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). SAT accounts for approximately 80% of the total body fat, whereas VAT constitutes 10–20% of the total body fat in men and 5–8% in women. SAT is primarily located in the hip and thigh regions, whereas VAT is situated around the internal organs in the abdominal cavity. There are significant endocrine and metabolic differences between these two types of adipose tissue. Generally, SAT comprises smaller adipocytes, a higher cell count, superior fat storage capacity, and greater secretion of lipocalin and leptin. By contrast, VAT exhibits increased vascularity with a lower capacity for vascular sprouting, heightened inflammation and immune cell infiltration, greater secretion of inflammatory factors, reduced insulin sensitivity, lower secretion of lipocalin, and a higher risk of metabolic abnormalities.¹⁷

Several factors contribute to the susceptibility of the VAT to metabolic dysfunction. VAT tends to stimulate an increase in β -adrenergic receptors while exhibiting fewer inhibitory α -adrenergic receptors, which results in diminished insulin-induced lipolysis inhibition and elevated serum free fatty acids (FFAs). Additionally, perivascular adipose tissue regulates vascular homeostasis in a paracrine manner by secreting various adipocytokines.^{18,19} Liu et al found that adipocytes secrete inflammatory factors such as interleukin-1 β (IL-1 β), IL-6, and tumor necrosis factor α (TNF- α), which promote endothelial cell inflammation, contributing to atherosclerosis and vascular injury.²⁰

Obesity and T2DM

The association between obesity, defined as excessive fat accumulation in the body, and various metabolic complications including insulin resistance, dyslipidemia, nonalcoholic fatty liver disease, prediabetes, and T2DM is widely acknowledged. However, this relationship is not linear; not all overweight individuals with similar obesity levels develop T2DM. For instance, not every individual categorized as obese exhibits adiposity, and some individuals with low body fat may develop T2DM as well.⁸

Obese individuals with a predominantly increased upper body fat distribution, such as abdominal subcutaneous fat, intra-abdominal fat, intrahepatic triglyceride content, and pancreatic fat, are at a higher risk of developing T2DM than those with increased lower body fat, particularly in the gluteofemoral region. Further studies have indicated that increased lower body fat is correlated with decreased plasma triglycerides, elevated high-density lipoprotein (HDL) cholesterol, reduced fasting glucose levels, improved oral glucose tolerance, enhanced insulin sensitivity, and a lower risk of T2DM.

This association may explain the differences in T2DM prevalence between Asian and white populations. Specifically, Asian individuals with T2DM tend to experience earlier onset, lower BMI, less weight gain, and a higher percentage of visceral fat. Hepatic insulin resistance is characterized by a reduction in insulin-stimulated hepatic gluconeogenesis signaling pathways, including insulin receptors and downstream mediators. High concentrations of lipids and specific lipid derivatives, such as ceramides and diacylglycerols (DAGs), can exert toxic effects on hepatocytes, a phenomenon known as “lipotoxicity.” Additionally, chronic hyperglycemia and excessive carbohydrate influx into the liver are

associated with the accumulation of hepatotoxic lipids, a condition referred to as “glucotoxicity.” This process involves the activation of lipogenic enzymes and the induction of endoplasmic reticulum (ER) stress, ultimately leading to steatosis and cell death.²¹

Adipose tissue functions as a major endocrine organ by releasing critical hormones and factors that regulate systemic metabolism, insulin sensitivity, and energy balance. Both deficiencies and excesses in adipose tissue can severely impair glucose homeostasis and lead to diabetes. Adipocytes from different depots, such as subcutaneous and visceral fat, exhibit distinct metabolic properties and expansion dynamics. White adipose tissue comprises not only mature adipocytes and precursor cells but also various other cell types associated with innervation and vascularization. In contrast, adipose tissue specializes in energy dissipation in the form of heat. Given the complexity of these structures, studies on glucose transport in adipocytes have typically focused on their biological contents. Compared with skeletal muscle, the contribution of adipocytes to glucose disposal is relatively minor.²²

Studies have demonstrated that obesity disrupts insulin activity and beta cell function, thereby facilitating the development of T2DM. Obese patients exhibit increased insulin secretion along with a diminished ability to extract and clear insulin from the portal vein and peripheral blood. Specifically, both basal and postprandial insulin levels, as well as insulin secretion rates, are higher in obese individuals than in their lean counterparts.²³ Although obese patients may not exhibit insulin resistance, they show elevated insulin secretion both in the basal state and after glucose intake. Notably, significant weight loss can reduce insulin secretion under both conditions. The mechanisms through which obesity leads to increased insulin secretion remain unclear; however, they may involve β -cell hyperresponsiveness to glucose, resulting in β -cell hyperplasia, as well as alterations in β -cell glucose catabolism and lipid signaling. Increased insulin secretion is recognized as an independent risk factor for prediabetes and T2DM, likely due to a chronic high demand for insulin, which can ultimately lead to β -cell failure.²⁴ Collectively, these alterations may contribute to impaired glycemic control and the onset of T2DM.

The adipose tissue expandability hypothesis, which addresses the limitations of the adaptive expansion of adipose tissue, elucidates how lipid overdeposition contributes to the development of obesity and its associated metabolic complications, including T2DM in individuals with obesity.²⁵ Physiologically, adipose tissue can expand or contract to adapt to various metabolic states, such as fasting or feeding. Continuous triglyceride accumulation in adipocytes during a positive energy balance necessitates the adaptive enlargement of these cells. However, the threshold for such adaptive changes differs among individuals, which is a key determinant of metabolic health heterogeneity among individuals with obesity. When the storage threshold is exceeded, excess energy is stored as lipids in non-adipose tissue, a phenomenon known as ectopic fat deposition. This occurs because of the impaired buffering capacity of adipose tissue against lipid influx and a compromised postprandial insulin-driven antilipolytic capacity, which limits the uptake of lipids from the circulation.²⁶

Microscopic evidence supports this hypothesis. Lipid disorders, characterized by elevated plasma free fatty acids (FFAs), ceramides, and triglycerides, act synergistically with glucose, a condition referred to as “glycolipotoxicity”,²⁷ or may interact with excess plasma amino acids, leading to what is termed “nutritionally induced metabolic stress”.²⁸ These conditions contribute to oxidative stress, mitochondrial dysfunction, and ER stress, ultimately resulting in β -cell dysfunction and apoptosis mediated by β -cell dedifferentiation. Importantly, elevated blood glucose levels are more detrimental to beta cells than FFAs. Even mildly elevated blood glucose levels (11 mg/dL) can induce phenotypic changes in gene expression that adversely affect β -cell function.²⁹

Adipose Tissue-Mediated Insulin Resistance

Research utilizing various mouse models of obesity has revealed that a series of complex and interrelated biological processes within adipose tissue contribute to systemic insulin resistance. These processes include: 1) adipocyte hypoxia resulting from insufficient oxygen delivery coupled with increased oxygen demand in adipocytes;^{30,31} 2) an elevated number and proportion of pro-inflammatory immune cells, such as macrophages and T-cells, within adipose tissue, along with heightened expression of the genes encoding pro-inflammatory proteins;³² 3) reduced production and secretion of lipocalin, an insulin-sensitizing hormone;³³ 4) increased lipolytic activity in adipose tissue, leading to greater release of FFAs into the circulation;³⁴ and 5) unfavorable alterations in the metabolism of exosomes derived from macrophages in adipose tissue.^{35–37}

These findings indicate that many of these changes are more closely associated with excessive obesity than with insulin resistance; however, it is plausible that these factors collectively contribute to the development of insulin resistance. Since the identification of pro-inflammatory cytokines produced by adipose tissue that contribute to insulin resistance in mice, and the subsequent discovery that obesity in humans correlates with the accumulation of macrophages in adipose tissue, it has been proposed that adipose inflammation serves as a significant driver of insulin resistance in obese individuals.³⁸

The relationship between visceral (intraabdominal) adipose tissue mass, insulin resistance, and the risk of T2DM, along with findings of increased counts of inflammatory macrophages and elevated expression of inflammatory genes in the subcutaneous abdominal adipose tissue of patients with metabolically unhealthy obesity compared with their “metabolically healthy obese” counterparts, supports the notion that increased visceral adiposity is a primary contributor to insulin resistance.³⁹ Other mechanisms of insulin resistance involving the adipose tissue include fibrosis, diHOME, and microRNA.⁴⁰ The mechanisms through which abnormal adipose tissue induces insulin resistance are summarized in [Figure 1](#).

Adipose Tissue Modulates Insulin Sensitivity

Glucose transporter 4 (GLUT4), a primary glucose transporter regulated by insulin, as a primary glucose transporter regulated by insulin, glucose transporter 4 (GLUT4) plays a crucial role in modulating adipocyte-mediated insulin sensitivity. This transporter is predominantly expressed in the adipocytes, skeletal muscle cells, and cardiac muscles. Human data indicate a strong correlation between GLUT4 levels in the adipose tissue and insulin sensitivity, with reduced GLUT4 levels serving as an early predictor of T2DM.^{41,42} Experimental studies involving specific overexpression⁴³ or knockdown⁴⁴ of GLUT4 in adipocytes further support the relationship between GLUT4 in adipose tissue and insulin sensitivity, demonstrating that alterations in GLUT4 levels can significantly affect systemic glucose metabolism, including that in the liver and skeletal muscle. Physiologically, insulin promotes glucose uptake into adipocytes through GLUT4. This process activates carbohydrate response element-binding protein (ChREBP),⁴⁵ a transcription factor that regulates the expression of the genes involved in adipogenesis and glycolysis. As a result, more glucose is utilized in the *de novo* synthesis of fat, leading to increased production of metabolically favorable lipids. These lipids help reduce adipose inflammation and enhance the insulin-stimulated translocation of GLUT4 to the cell membrane, thereby facilitating the action of insulin and improving glycemic control.

Research from both human and experimental studies has demonstrated a strong correlation between ChREBP or adipogenic gene expression and insulin sensitivity in obese but non-diabetic individuals,⁴⁶ independent of BMI.⁴⁷ However, in insulin resistance and obesity, GLUT4 expression in adipocytes is downregulated,⁴⁸ leading to elevated levels of retinol-binding protein 4 (RBP4) in both adipocytes and serum.^{49–51} This increase in RBP4 levels contributes to increased adipose tissue inflammation, increased lipolysis, and impaired translocation of GLUT4 to the plasma membrane, thereby increasing the risk of T2DM. The role of RBP4 in promoting adipose tissue inflammation is mediated through toll-like receptor 4 (TLR4) and several other pathways involving the activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome. Specifically, RBP4 stimulates the production of pro-inflammatory factors by macrophages via the Jun N-terminal kinase (JNK)-dependent pathway, which indirectly impairs insulin signaling. Additionally, reduced expression of ChREBP in insulin-resistant states leads to decreased *de novo* synthesis of fat and reduced production of metabolically favorable lipids, resulting in increased inflammation within the adipose tissue and impaired physiological effects of insulin.⁵²

As a result, increased glucose transport to adipocytes enhances insulin sensitivity, which correlates with greater utilization of glucose in fatty acid synthesis regulated by ChREBP. This is supported by observations in transgenic mice with specific overexpression of GLUT4 in adipocytes, in which enhanced *de novo* synthesis of fat resulting from increased glucose transport was found to be essential for improved glucose tolerance.⁴⁵ Consequently, an increase in *de novo* fat synthesis within the adipose tissue may lead to a higher production of metabolically beneficial lipids. To validate this concept, untargeted lipidomic analyses performed on adipose tissue from transgenic mice specifically overexpressing GLUT4 in adipocytes identified branched FAHFs with antidiabetic and anti-inflammatory properties.^{53–55}

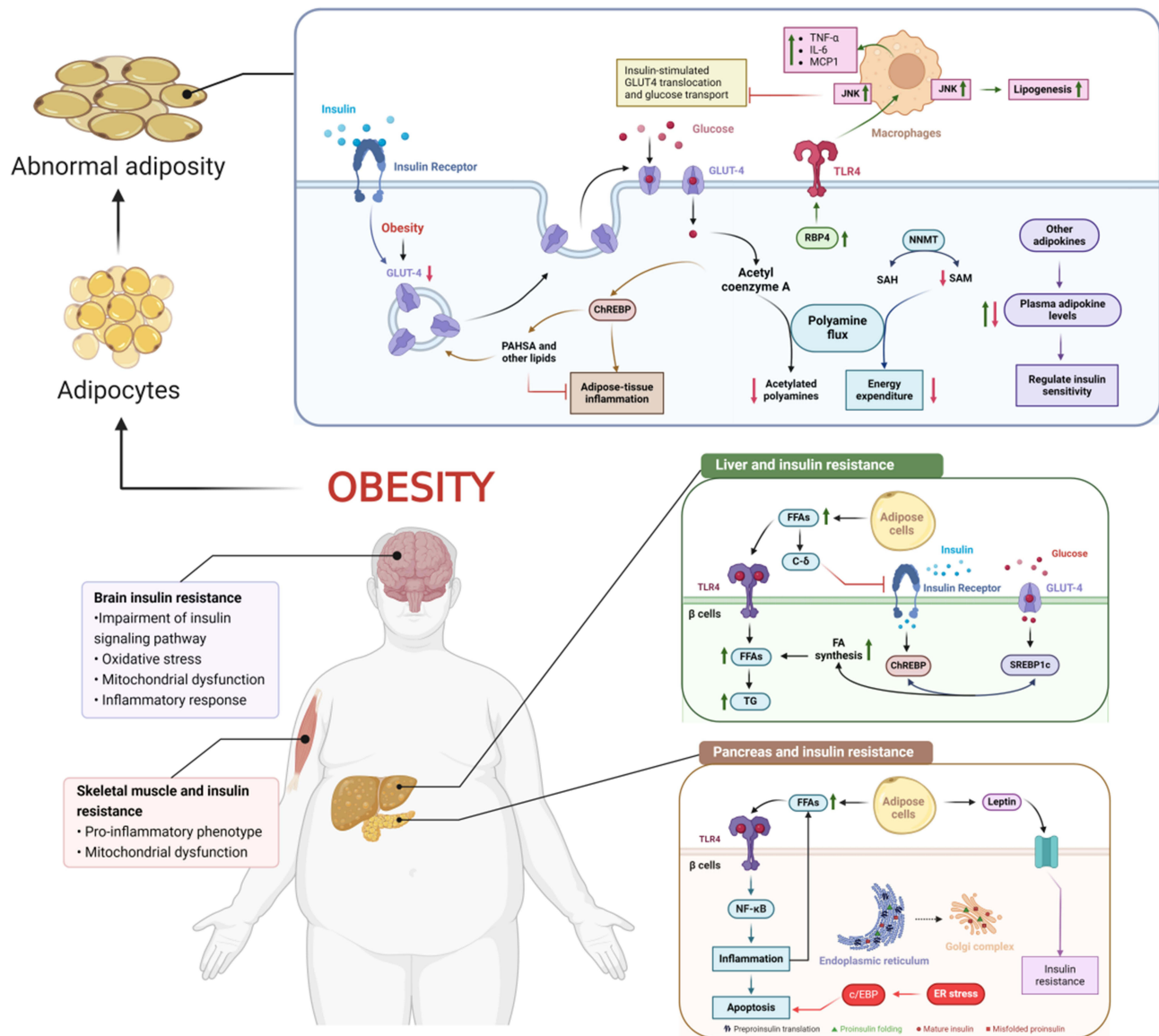


Figure 1 Overview of Mechanisms Leading to Obesity-Induced Insulin Resistance. This figure illustrates how obesity leads to insulin resistance through various metabolic pathways: Changes in Adipose Tissue: Obesity causes adipocytes and macrophages to secrete inflammatory factors (such as TNF- α , IL-6, MCP-1), activating the JNK pathway, which results in adipose tissue inflammation and increased lipogenesis. Brain Insulin Resistance: Obesity impairs insulin signaling in the brain, leading to damaged insulin signaling pathways, increased oxidative stress, mitochondrial dysfunction, and inflammatory responses. Skeletal Muscle Insulin Resistance: Obesity induces a pro-inflammatory phenotype and mitochondrial dysfunction in skeletal muscle. Liver Insulin Resistance: Obesity causes adipocytes to secrete free fatty acids, leading to increased fatty acid synthesis in the liver; impaired insulin signaling, and ultimately reduced glucose transport. Pancreatic Insulin Resistance: Obesity results in increased levels of free fatty acids and inflammatory factors, causing pancreatic cell apoptosis, decreased insulin secretion, and endoplasmic reticulum stress.

FAHFAs

FAHFAs are widely distributed in humans, animals, and plants and exhibit a variety of isomers. At least 51 families of FAHFAs have been identified, with the highest concentrations found in mammalian subcutaneous white and brown adipose tissues. Administration of FAHFAs has been shown to stimulate glucagon-like peptide 1 and insulin secretion, while reducing obesity-related inflammation in white adipose tissue (WAT) in mice through G protein-coupled receptor 120-dependent signaling.^{53–55} Additionally, n-3 polyunsaturated fatty acids (PUFAs) demonstrate anti-inflammatory effects via G protein-coupled receptor 120 and several other signaling pathways, contributing to enhanced insulin secretion and increased insulin sensitivity in obese mice. Although these findings suggest the potential benefits of FAHFAs in the context of T2DM, the lack of randomized controlled trials (RCTs) indicates that the actual clinical benefits remain a subject of debate.

In both the physiological state of fasting and the pathophysiological state of obesity induced by a high-fat diet, the concentrations of FAHFAs are tightly regulated by tissue type and isomer specificity.^{56–60} Research has demonstrated that multiple FAHFA subfamilies exhibit anti-inflammatory effects, including palmitic acid esters of hydroxystearic acids (PAHSAs), palmitoleic acid esters of hydroxystearic acids (POHSAs), oleic acid esters of hydroxystearic acids (OAHSAs), stearic acid esters of hydroxystearic acids (SAHSAs), and linoleic acid esters of hydroxy linoleic acid (LAHLAs).^{54,60,61} However, it is important to note that not all studies support the beneficial role of PAHSAs,^{62,63} and not all isomers of FAHFAs demonstrate positive effects. Additionally, there is significant heterogeneity in their biological effects,^{60,64} which may be attributed to differences in their genetic backgrounds.

Association Between FAHFA and Insulin Resistance & DM

PAHSA levels are also strongly associated with insulin sensitivity. Regardless of the presence or absence of T2DM, the concentrations of various PAHSA isomers in the serum and adipose tissue are reduced in individuals with insulin resistance. Additionally, the serum levels of total PAHSA and FAHSA, particularly oleic acid ester of 9-hydroxystearic acid (9-OASHA), are lower in obese individuals than in their non-obese counterparts. In a follow-up study involving patients who underwent sleeve gastrectomy, weight loss, and maintenance of improved metabolic markers, only the 9-OASHA levels were elevated.⁶⁵ Further research has shown that PAHSAs can directly enhance glucose-stimulated insulin secretion, with 5-PASHA demonstrating the ability to restore normal pulsatility of insulin secretion in patients with T2DM.^{66–68}

Building on the findings of human studies, the mechanisms of action of FAHFA have been investigated in experimental animal models. Although some FAHFA isoforms enhance insulin-stimulated glucose transport to adipocytes,⁶⁰ this effect is not universal among all isoforms. Both 5- and 9-PAHSA were found to increase glucose transport to adipocytes by facilitating insulin-mediated GLUT4 translocation.⁵³ However, the roles of 5- and 9-PAHSA differed between mice fed a standard chow diet and those fed a high-fat diet. In insulin-resistant chow-fed mice, both 5- and 9-PAHSA improved insulin sensitivity and glucose-stimulated insulin secretion, with the latter likely resulting from the stimulatory effect of PAHSA on glucagon-like peptide-1 (GLP-1) in enteroendocrine cells.^{53,66} Conversely, in high-fat-fed mice, 5- and 9-PAHSA did not exhibit beneficial effects on insulin secretion, but demonstrated insulin-sensitizing properties that promote glucose homeostasis.⁵⁹ Specifically, long-term administration of 5- and 9-PAHSA increases systemic and hepatic insulin sensitivity, enhances glucose uptake in skeletal muscle and cardiac tissues, and facilitates glycolysis in mice with obesity induced by a high-fat diet.⁵⁹ The insulin-sensitizing effects of PAHSAs in the context of HFD-induced insulin resistance may stem from their anti-lipolytic properties, as lipolytic activity is heightened in this state owing to increased adipose inflammation. Further studies are required to elucidate the mechanisms by which PAHSAs exert their antilipolytic effects.

The discovery of the insulin-sensitizing properties of PAHSAs is significant because insulin resistance is a major pathogenic factor in T2DM. It is widely recognized that there are very few drugs available that primarily function as insulin sensitizers for T2DM treatment, and their use is often limited due to safety concerns and side effects, such as those associated with thiazolidinediones.⁶⁹ Moreover, in macrophages derived from the adipose tissue of insulin-resistant mice, 9-PAHSA has been shown to inhibit the lipopolysaccharide-induced maturation of dendritic cells, antigen presentation, and pro-inflammatory cytokine production.⁵³ Additionally, the decosahexaenoic acid ester of 13-hydroxyoctadecadienoic acid (13-DHAHLA) reduces has been found to reduce macrophage activation.⁵⁴

Studies have established that PAHSA treatment in non-obese diabetic (NOD) mice delays the onset of type 1 diabetes mellitus (T1DM) and significantly prolongs their survival.⁷⁰ The beneficial effects observed in NOD mice can be attributed to two primary mechanisms: immune cell modulation and direct protective effects of PAHSAs on pancreatic islet cells. Specifically, PAHSA treatment reduced the infiltration of pro-inflammatory immune cells into pancreatic islets and promoted the proliferation of β -cells in vivo.⁷⁰ Furthermore, PAHSAs alleviate ER stress in human pancreatic islets and can partially restore insulin secretion even when glucose-stimulated insulin secretion is completely inhibited. Recent findings suggest that the protective effects of PAHSAs on pancreatic islets are primarily mediated by the prevention or reversal of cellular senescence, with β -cell senescence being a significant factor in both T1DM and T2DM.⁷¹

Determinants of FAHFA Concentration

The concentration of FAHFA in the serum is influenced by dietary intake as well as the relative rates of FAHFA synthesis and hydrolysis. Notably, the levels of FAHFA isomers in food do not always correspond to the serum or tissue levels observed in individuals. Short-term overconsumption of a high-calorie diet, particularly one high in saturated fats, has been shown to increase serum FAHFA levels.⁶⁵ Recent studies have indicated that adipose triglyceride lipase is responsible for synthesizing FAHFA and plays a critical role in determining FAHFA concentrations *in vivo*.⁷² In mice with a specific knockout of adipose triglyceride lipase in adipocytes, the levels of both endogenous and newly synthesized FAHFAs were reduced by 80–90%.⁷²

Further investigations have revealed that mutations in adipose triglyceride lipase can result in cardiomyopathy, skeletal muscle myopathy, and other abnormalities associated with lipid overload in tissues, including neutral lipid deposition myopathy.^{73,74} However, whether reduced FAHFA production directly contributes to these phenotypes remains unclear. In terms of FAHFA hydrolysis, four hydrolases have been identified in mammals, including carboxylester lipase.⁷⁵ Mutations in carboxylester lipases are linked to the onset of late adolescent diabetes mellitus type 8 (MODY8).⁷⁶ In this patient subset, mutations in the carboxylester lipase led to increased hydrolysis of 9-PAHSA. Experimental studies involving CXL knockdown of carboxylester lipase in the pancreatic tissue have demonstrated a significant decrease in the hydrolysis of 9-PAHSA. Consequently, excessively low levels of FAHFA *in vivo* may also contribute to diabetic phenotypes.

Interventions for Weight Loss or Improving Ectopic Fat Deposition

In a subset of patients with diabetes, natural disease progression often follows a trajectory from obesity to metabolic syndrome, prediabetes, diabetes, and, ultimately, end-stage T2DM, characterized by the presence of microvascular and macrovascular complications. The latest guidelines from the American Diabetes Association (ADA) recommend that in patients with T2DM who are also overweight or obese, moderate weight loss can enhance glycemic control and reduce the need for glucose-lowering medications. Significant weight loss is associated with considerable reductions in HbA1c and fasting glucose levels, which may facilitate sustained diabetes remission.⁷⁷ Recent studies have indicated that patients with T2DM who achieve lower body weight through dietary interventions can achieve disease.⁷⁸ A summary of the treatment strategies for obesity is presented in [Figure 2](#).

Lifestyle Intervention and Ectopic Fat Deposition

Lifestyle interventions are essential for preventing and treating metabolic diseases. During fasting and exercise, triglycerides stored in adipose tissue are gradually hydrolyzed into non-acylated fatty acids and glycerol by adipose triacylglycerol lipase and hormone-sensitive lipase to meet the body's energy demands. According to the twin cycle hypothesis of the liver and pancreas, reducing excess triglycerides in these organs can restore energy homeostasis, which may in turn promote glucose homeostasis.⁷⁹ In terms of dietary composition, the intake of saturated fatty acids is a significant contributor to ectopic fat deposition, whereas that of unsaturated fatty acids is negatively associated with such deposition.⁸⁰ Furthermore, the consumption of insoluble dietary fiber has been linked to reductions in VAT, lower fasting glucose levels, and improved insulin resistance in individuals with impaired glucose tolerance.⁸¹

The DiRECT study evaluated the impact of an intensive dietary intervention, which included complete dietary substitution and the discontinuation of hypoglycemic and antihypertensive medications, in 306 patients with T2DM (disease duration ≥ 6 years, BMI: 27–45 kg/m²). After two years of follow-up, the percentage of participants achieving a weight loss of at least 5 kg was 11% (17 out of 149) of the participants in the intervention group achieved a weight loss of at least 5 kg, compared to only 2% (2 out of 149) in the control group.⁸² A subsequent post hoc analysis conducted on the complete follow-up data of 272 subjects revealed a correlation between the magnitude of weight loss and the rate of diabetes remission. Notably, at the 24-month mark, diabetes remission was achieved in 70% of the participants who lost at least 15% of their body weight.⁸³ In contrast, remission rates for participants who lost 10–15 kg, 5–10 kg, and less than 5 kg were 60%, 29%, and 5%, respectively.⁸³ Furthermore, among those who did not achieve diabetes remission, the participants in the intervention group experienced a greater reduction in HbA1c levels and a decreased need for glucose-

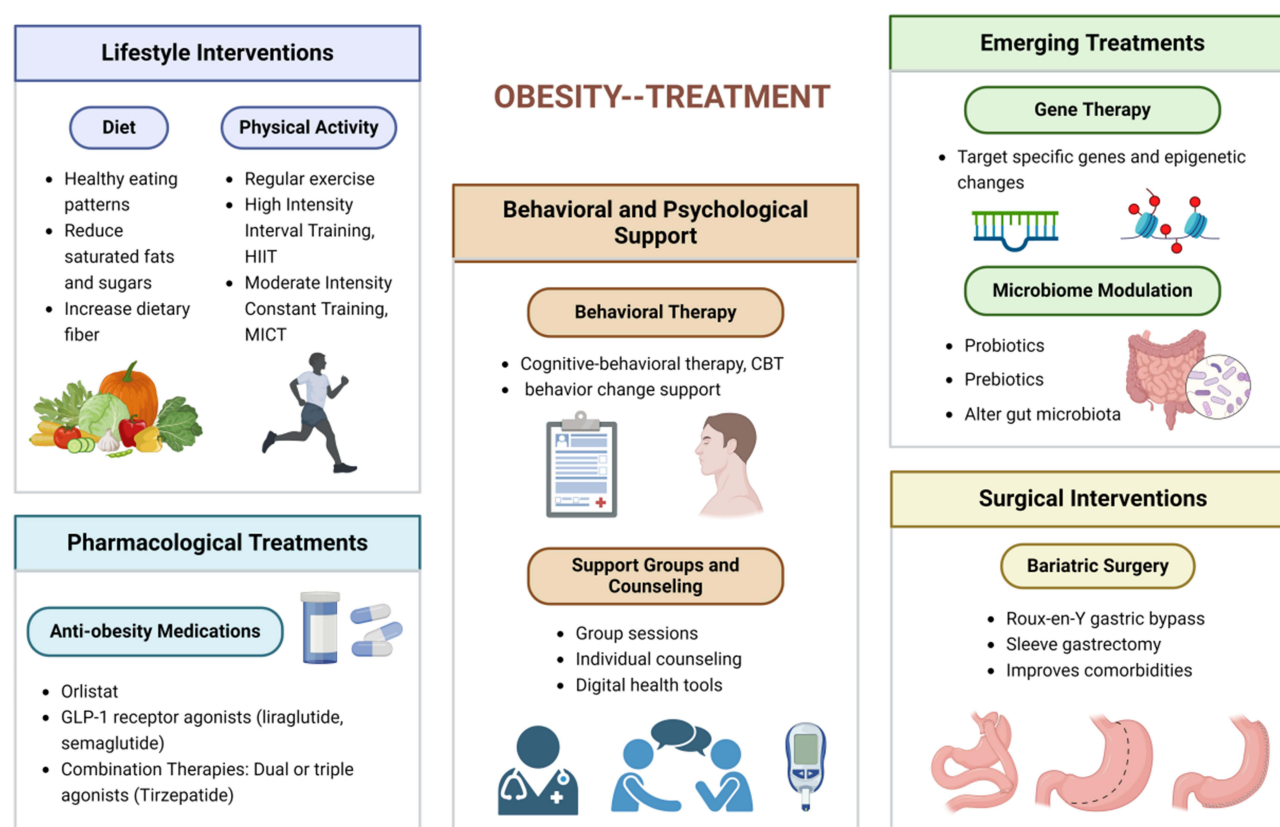


Figure 2 Comprehensive Strategies for Treating Obesity. This figure provides an overview of various treatment strategies for obesity, categorized into five main approaches: Lifestyle Interventions, Pharmacological Treatments, Behavioral and Psychological Support, Surgical Interventions, and Emerging Treatments.

lowering medications. The ADA guidelines support the notion that overweight or obese patients with DM can benefit from any degree of weight loss. Specifically, a 3%–7% reduction in baseline weight can improve glycemic control and cardiovascular risk factors, whereas sustained weight loss of more than 10% is typically associated with greater benefits, including potential disease improvement, T2DM remission, and enhancements in long-term cardiovascular outcomes and mortality.⁷⁷ In a recent meta-analysis involving 1101 individuals with prediabetes or T2DM, intermittent fasting was shown to reduce body weight (weighted mean difference: −4.56 kg), BMI (weighted mean difference: −1.99 kg/m²), and HbA1c (weighted mean difference: −0.81%). However, compared with calorie-restricted diets, intermittent fasting did not significantly affect glycemic indices, visceral fat, lipid profiles, or blood pressure.⁸⁴ Another study found that intermittent fasting and early time-restricted eating significantly improved postprandial glucose metabolism in individuals at a high risk of T2DM.⁸⁵ A randomized controlled trial assessing the safety and efficacy of three non-consecutive intermittent fasting sessions per week over 12 weeks reported a change in HbA1c of −7.3 mmol/mol in the intermittent fasting group, compared to a change of 0.1 mmol/mol in the control group.⁸⁶

Skeletal muscle contraction and exercise facilitate translocation of GLUT4 to the plasma membrane of skeletal muscle cells, thereby enhancing glucose uptake. This physiological process requires stimulation by either insulin or exercise. Skeletal muscle cells contain two distinct GLUT4 pools, and exercise-mediated GLUT4 translocation notably occurs independent of insulin stimulation.

Additionally, skeletal muscles secrete myokines such as irisin, myonectin, IL-15, and O-GlcNAcylation, which may play a role in regulating fatty acid oxidation, glycogen synthesis, and insulin sensitivity.⁸⁷ Recent studies demonstrated that moderate-intensity training enhances the secretion of IL-15 from skeletal muscle cells, leading to increased fatty acid oxidation, improved glycogen synthesis, and reduced inflammation.⁸⁸ Furthermore, exercise stimulates mitochondrial elongation, thereby enhancing mitochondrial function.⁸⁹ Consequently, exercise is a vital strategy for improving adipose tissue function and mitigating insulin resistance. Findings from a meta-analysis indicated that exercise reduces VAT and

is more effective than pharmacological interventions including orlistat, liraglutide, rimonabant, gemfibrozil, metformin, rosuvastatin, ezetimibe, and empagliflozin.⁹⁰ However, the optimal form of exercise to decrease visceral fat is still debated. A meta-analysis found that high-intensity interval training and moderate-intensity aerobic exercise were effective in reducing VAT, whereas resistance exercise, aerobic exercise combined with resistance training, and sprint interval training did not demonstrate significant benefits.⁹¹ Conversely, a more recent meta-analysis concluded that aerobic exercise at moderate intensity, resistance training, a combination of both, and high-intensity interval training were all beneficial in reducing VAT.⁹² Therefore, further research is necessary to identify the most effective exercise modality for guiding weight loss.

Considering the metabolic benefits of with intermittent fasting and time-restricted eating, researchers have investigated the efficacy of combining exercise training with these dietary approaches. A meta-analysis involving 568 participants examined the effects of combining time-restricted eating with exercise training compared with exercise training alone. The findings indicated that this combination resulted in a reduction in body mass (mean difference: -1.86 kg) and fat mass (mean difference: -1.52 kg), and improvements in lipid metabolism. However, this did not yield additional benefits for glucose profiles.⁹³ Similarly, another meta-analysis assessed the combination of exercise training and intermittent compared to exercise training or intermittent fasting alone. This analysis reported reductions in body weight (weighted mean difference: -3.03 kg), BMI (weighted mean difference: -1.12 kg/m²), and visceral fat (standard mean difference: -0.34). Nevertheless, it failed to demonstrate significant differences in cardiometabolic health markers when compared to exercise training or intermittent fasting alone.⁹⁴

Unfortunately, lifestyle interventions often prove inadequate over the long term and fail to achieve the desired outcomes for both clinicians and patients. Research has shown that most lifestyle interventions result in gradual weight loss over the first six months, followed by a plateau and subsequent rebound within 1–3 years.⁹⁵ Although continuous monitoring, lifestyle counseling, and anti-obesity medications can aid in maintaining weight loss, the long-term response rate to lifestyle interventions remains low.^{96,97} As a result, many patients require additional strategies to achieve significant weight loss and sustain it over time.

Bariatric Surgery

According to a statement issued in 2022 by the American Society of Metabolic and Bariatric Surgery (ASMBS) and the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO),^{98,99} surgery is a well-established and effective treatment approach for obesity.

Before surgery, patients should be thoroughly assessed for obesity indicators including BMI, waist circumference, hip circumference, and visceral fat area. Additionally, evaluations should include obesity-related comorbidities such as prediabetes, T2DM, and hypertension as well as psychosocial factors such as depression and nutritional status, including vitamin and micronutrient levels.^{100–102} In postoperative management, the principles of rapid rehabilitation surgery should be implemented to promote swift recovery.¹⁰³ It is essential to regulate fluid intake within the first 3 days post-surgery as well as to monitor dietary intake for the subsequent three months, with a strong emphasis on protein supplementation and nutritional monitoring, including vitamin and mineral supplementation.^{104–107} Whenever feasible, long-term nutritional and health monitoring should be established to encourage patient self-management and to address poor eating habits. Although bariatric surgery offers significant metabolic benefits, it is important to acknowledge its potential risks, including an increased likelihood of suicide, self-harm, emotional eating, and gastrointestinal complications such as bile disorders, gastritis, small bowel obstruction, gastric stenosis, and gastric perforation.^{108,109}

Studies have demonstrated that surgical intervention can significantly enhance the rate of diabetes remission in patients with obesity and T2DM, leading to improved glycemic control and a reduction in long-term vascular complications. The rates of diabetes remission following bariatric surgery are notable, with 5-year and 20-year remission rates reaching 75% and ranging from 37% to 51%, respectively.^{110,111} Furthermore, bariatric surgery is effective in addressing various metabolic complications including hypertension and dyslipidemia. Research indicates that the average weight loss associated with different interventions is as follows: medication results in a weight loss of 1–10%, Roux-en-Y gastric bypass (RYGB) surgery yields a loss of 22–37%, and sleeve gastrectomy leads to an average loss of approximately 19%.^{112–114} Additionally, a prospective cohort study with an extended follow-up period revealed that participants who

underwent Roux-en-Y gastric bypass surgery experienced greater sustained weight loss and a lower incidence of T2DM compared to those who did not undergo surgery.^{111,115} Bariatric surgery also reduced both microvascular and macrovascular events, ultimately enhancing patients' quality of life.¹¹⁶ The benefits of bariatric surgery extend beyond weight loss; it also induces significant changes in hormone levels. This surgical intervention can exert a direct hypoglycemic effect by regulating appetite through the gastrointestinal tract, modulating the gut-brain axis, and influencing feeding behavior.¹¹⁷

Pharmacological Treatment

Given the advantages of weight loss in disease management, medications that promote weight loss are prioritized, when feasible, for patients with T2DM who are also overweight or obese.

Although several medications have been approved by the US Food and Drug Administration (USFDA) for the long-term management of obesity, only orlistat has been approved for obesity management in China. A comprehensive overview of medications approved globally has been provided in previous reviews.⁸ Orlistat reduces fat absorption by approximately 30% by binding to the active site of lipase, thereby inhibiting its function. This mechanism prevents the absorption and hydrolysis of fats excreted in feces. Despite its effectiveness in reducing VAT, the adverse gastrointestinal effects associated with orlistat, such as steatorrhea, limit its widespread adoption.¹¹⁸ Although the efficacy and safety of liraglutide and semaglutide for weight loss in overweight or obese Chinese adults have not been systematically evaluated, both medications have been formally approved for weight loss in several countries, including the United Kingdom, Europe, and North America. The STEP series of clinical studies demonstrated the significant weight loss efficacy of semaglutide, with an average weight reduction of 15%.¹¹⁹ In the STEP 2 trial, a 68-week clinical study involving 1,210 patients with T2DM who receiving 2.4 mg of semaglutide once weekly experienced a weight loss of 9.6%, whereas those receiving 1.0 mg of semaglutide once weekly achieved a weight loss of 6.9%, along with a significant improvement in HbA1c levels. Notably, 68% of participants with a baseline HbA1c level of 8.0% achieved a reduction to $\leq 6.5\%$.¹²⁰

Dual and triple agonists have been developed to replicate the endogenous coordinated postprandial release of various gut hormones by leveraging the biological complementarity of gut peptides to regulate food intake. Tirzepatide, a dual GLP-1 and GIP receptor agonist, has received FDA approval for treating overweight and obesity as well as for managing T2DM as a long-term obesity intervention. The SURPASS clinical trial assessed the effects of 5, 10, and 15 mg doses of tirzepatide compared with 1 mg semaglutide in adults with T2DM who were also receiving metformin. The results indicated that all doses of tirzepatide produced greater weight loss and reduction in HbA1c levels than semaglutide.¹²¹ Notably, approximately 90% of participants receiving the 15 mg dose of tirzepatide achieved an HbA1c level of less than 7.0%, with approximately half reaching an HbA1c level of less than 5.7%. Furthermore, tirzepatide demonstrated superior glucose-lowering effects compared with basal insulin therapy, as evidenced in the SURPASS-3 and SURPASS-4 studies,^{122,123} and was also effective as an adjunct therapy to additional postprandial insulin in the SURPASS-6 trial.¹²⁴ The SURPASS-5¹²⁵ study highlighted its efficacy as an add-on therapy to improve basal insulin levels. In the SURMOUNT-1 study, which focused on the overweight population, participants treated with the highest dose of tirzepatide (15 mg) experienced an average weight loss of 23 kg, compared to an average loss of 16 kg in those receiving the lowest dose (5 mg) and only 3 kg in the placebo group.¹²⁶ Additionally, a Phase II trial evaluated the effects of retatrutide, a triple glucagon-like peptide-1 (GLP-1)/ gastric inhibitory polypeptide (GIP)/ glucagon (GCG) agonist, in overweight or obese patients with T2DM. This trial reported a 2.02% reduction in HbA1c levels at 24 weeks, and an average weight loss of 17.1 kg at 36 weeks.¹²⁷

In addition to anti-obesity medications, four of the twelve classes of hypoglycemic agents utilized for the treatment of T2DM are known to promote weight loss: sodium-dependent glucose transporter 2 (SGLT2) inhibitors, GLP-1 receptor agonists, metformin, and amylin analogs. Although there is considerable variability in individual responses, the average weight loss induced by these medications in adults with T2DM is modest, typically ranging from 1.4 to 1.9 kg, along with a reduction in HbA1c of 0.4 to 0.9% over a treatment period of 6 to 12 months.^{128–130} Research indicates that semaglutide, administered at a dosage of 1 mg per week, results in greater weight loss and HbA1c reduction than exenatide at 2 mg, canagliflozin at 300 mg, and liraglutide at 1.2 mg per week.¹³¹ Moreover, semaglutide was associated with a 26% reduction in the risk of major adverse cardiovascular events.¹³² A recent meta-analysis highlighted

semaglutide as the most effective agent for weight loss, followed by phentermine and topiramate, with both medications exhibiting similar risks of adverse events.¹³³

Amylin, a hormone produced by the pancreas, increases satiety and decreases glucagon levels. A long-acting amylin analog, cagrilintide, recently demonstrated the ability to reduce body weight by approximately 10% when administered weekly over a 26-week study period.¹³⁴ The combination of cagrilintide and semaglutide, referred to as CagriSema, is currently being evaluated for its efficacy in treating overweight and obese patients, both with and without T2DM, as a part of the REDEFINE program.¹¹⁹

Traditional Chinese Medicine

Traditional Chinese Medicine (TCM) has played a significant role in clinical practice and treatment across East Asian countries, largely because of the potential side effects of pharmacological treatments, such as hypoglycemia, as well as cultural, traditional, and social norms. TCM has been shown to contribute to the management of T2DM by reducing insulin resistance, exerting anti-inflammatory effects, alleviating oxidative stress, improving lipid metabolism, and regulating the gut microbiota. Specifically, Gegen Qinlian Decoction (GQD) has been shown to significantly reduce hepatic mitochondrial acetyl coenzyme A levels and phosphatidylcholine activity, leading to decreased insulin resistance (IR) within the liver.¹³⁵ Puerarin has been found to significantly inhibit the activity of tyrosine phosphatase 1 B, thereby enhancing insulin receptor sensitivity and reducing IR.¹³⁶ Similarly, extracts from *Scutellariae radix* and *Coptidis rhizoma* have been shown to significantly inhibit gluconeogenesis and glycogenolysis, while upregulating insulin receptor substrate 1 and GLUT2, effectively ameliorating IR in the liver.¹³⁷

Saffron supplementation has been reported to reduce mRNA levels of pro-inflammatory factors such as TNF- α and IL-6, while simultaneously increasing the mRNA expression of anti-inflammatory factors like IL-10 in patients with T2DM. Curcumin has been demonstrated to decrease malondialdehyde levels and increase glutathione peroxidase (GSH-Px) and total oxidative capacity by modulating the peroxisome proliferator-activated receptor γ (PPAR- γ) signaling pathway.¹³⁸ Similarly, resveratrol significantly increased GSH-Px and catalase levels in the liver.¹³⁹ Ganoderma lucidum polysaccharides have been effective at elevating GSH-Px, hepatic catalase, and superoxide dismutase (SOD) levels while decreasing malondialdehyde by upregulating the nuclear transcription factor 2-related factor 2/heme oxygenase-1 signaling pathway.¹⁴⁰ Quercetin reduces lipid, cholesterol, triglyceride, and bile acid deposition by activating the Farnesyl X receptor-1 (FXR-1)/transmembrane G protein-coupled receptor-5 (TGR-5) signaling pathway.¹⁴¹ Tangduqing granules, which consist of *Astragalus*, *Epimedium*, *Rhubarb*, and pseudo-ginseng root, have shown comparable efficacy primarily by modulating the PPAR- γ /diacylglycerol acyltransferase 2 (DGAT2) signaling pathway.¹⁴² The safety and efficacy of the aforementioned natural extracts, decoctions, and Chinese patent medicines (excluding *Ganoderma lucidum* polysaccharides) have been extensively documented in the literature.^{143–147}

A significant link has been established between the composition of the gut microbiota and development of T2DM. Growing evidence suggests that TCM can enhance glucose metabolism by modifying the characteristics of the gut microbiota. For instance, *Astragalus* has been shown to increase the abundance of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* in the gut flora of mice with T2DM, thereby slowing disease progression.¹⁴⁸ Berberine, a key ingredient in TCM for treating T2DM, was evaluated in a 12-week randomized controlled clinical trial, where it increased the abundance of *Bacteroides* spp. and Proteobacteria, similar to the effects of metformin.¹⁴⁹ Additionally, berberine enhances the diversity of the gut microbiota, induces cell death in harmful bacteria, modulates tryptophan metabolism, and improves the intestinal barrier. Similar to metformin, berberine also upregulates the mitogen-activated protein kinase (MAPK) pathway, promoting catabolism, leading to glycolysis, weight loss, and reduced IR.¹⁵⁰

GQD, which includes Chinese goldthread rhizomes, *Scutellaria*, lobed kudzu root, membranous milkvetch root, thin leaf ginseng, peony, and turmeric, has effects on intestinal microbial structure that are broadly similar to those of berberine. However, unlike berberine, GQD also increases the abundance of butyrate-producing bacteria, such as *Faecalibacterium*, *Bifidobacterium*, and *Gemmiger*. These changes contributed to reduced intestinal inflammation and improved glucose metabolism.¹³⁷ Animal studies demonstrated that both GQD and berberine increase plasma short-chain fatty acids and decrease fasting insulin levels.¹⁴³ Further research indicated that GQD enhances the abundance of *Faecalibacterium prausnitzii*, which is negatively correlated with levels of fasting blood glucose, 2-hour postprandial

blood glucose, and glycated hemoglobin, and positively correlated with insulin response.¹⁵¹ Another formulation used for the treatment of T2DM, JinQi Jiangtang (JQJT), contains Huanglian, membranous milkvetch root, and honeysuckle flower. A randomized controlled clinical trial involving 400 individuals with prediabetes and T2DM demonstrated that JQJT reduced the incidence of T2DM as well as blood glucose levels, triglyceride levels, proteinuria, and IR.¹⁵² Animal studies have shown that JQJT increases the abundance of *Akkermansia* spp. and decreases the abundance of *Desulfovibrio* spp. Notably, the abundance of *Akkermansia* spp. is associated with reduced inflammation in overweight populations.¹⁵³

Limitations

Poor control of DM is often linked to insulin resistance, which is influenced by a variety of factors, including genetics, obesity, environmental factors, and hormone levels. This study aimed to review the relationship between adipose deposits and insulin resistance. However, it has certain limitations.

1. Incomplete Understanding of Adipose Tissue and Diabetes: The association between adipose tissue and diabetes has not yet been fully elucidated. Although it is known that adipose deposits contribute to the development of T2DM, pancreatic β -cell depletion, and insulin resistance, such as the close relationship between hepatic steatotoxicity and insulin resistance, the specific roles of different types of adipose tissue in diabetes require further investigation. This knowledge is essential to substantiate the benefits of fat loss in obese patients and inform effective fat reduction programs.

2. Unclear Mechanisms of FAHFAs: Fatty acid esters of hydroxy fatty acids (FAHFAs) exhibit promising potential for enhancing insulin sensitivity in mice; however, their role in lipolysis remains unclear. Additionally, although FAHFAs have been shown to prevent or even reverse β -cell senescence much of the supporting research consists of in vitro experiments or preclinical studies in animal models. Consequently, these results may not directly translate to human physiology because of inherent differences in metabolism and microenvironment.

3. Challenges in Reducing Fat Deposition in Patients with T2DM: Although the reviewed studies indicate benefits in reducing fat deposition among patients with T2DM, it is crucial to acknowledge the limitations and challenges involved. Alternative modalities such as pharmacological and surgical treatments often present varying degrees of side effects. TCM has demonstrated better clinical efficacy; however, TCM preparations frequently face constraints related to compounding, ingredient extraction, and a lack of standardized prescriptions. Furthermore, the inability to harmonize guidelines and regulatory frameworks stemming from differences in medical standards, ethnicities, and dietary structures across regions restricts the clinical application of certain weight loss approaches.

Conclusion and Future Directions

Recent studies have confirmed that obesity and T2DM are highly correlated, and our review highlights the association between diabetes and obesity. With advances in the development of peptide therapies, the treatment of obesity and T2DM has entered a new era, with a number of patients with early stage T2DM experiencing gains as drugs that help stabilize and significantly reduce weight continue to be developed. In addition, we believe that FAHFA is a research direction worthy of continued development, and recent studies on the starting family have shown that they have beneficial effects on insulin sensitivity, islet protection, and insulin action, especially in terms of improving insulin sensitivity. Therefore, they have the potential to become a new strategy for the treatment of T2DM. However, not all FAHFA isomers exhibit beneficial effects in T2DM. Thus, further studies are needed to elucidate the biological effects of FAHFAs to develop new therapeutic strategies for T2DM.

In addition, in China and parts of East Asia, as further research continues into TCM, there seem to be more options for treating T2DM. Moreover, both preclinical and clinical studies have confirmed the benefits of TCM; in the future, more studies focusing on TCM are required to identify its effective pharmacological components for treating T2DM, which is also expected to be a new strategy for the treatment of T2DM.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests.

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