Diabetes, Metabolic Syndrome and Obesity

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REVIEW

The Central Role of Lipid Metabolism Disorders in Diabetes Mellitus: Mechanisms, Clinical Manifestations, and Emerging Therapeutic Strategies

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Abstract: Diabetes mellitus, as a metabolic disease, is characterized by dual metabolic disorders of glucose and lipids. Effective prevention and control of the progression of diabetes is the key to its treatment. Dyslipidemia in Diabetes is not merely a simple increase in lipid levels; it also involves the disordered coordination of multiple lipoprotein systems and molecular pathways, serving as both a driver and accelerator for diabetes. Lipid metabolism disorders directly magnify the harm of hyperglycemia, especially for the cardiovascular and cerebrovascular systems, and are one of the core pathological links of diabetes. Mechanisms involve multiple interactions such as insulin resistance and enhanced lipolysis, increased lipid synthesis and modification induced by hyperglycemia, oxidative stress and inflammatory responses, and hormonal and signaling pathway imbalances. Lipid metabolism disorders not only accelerate large vessel lesions such as atherosclerosis, but also promote microvascular damage (such as nephropathy and retinopathy) through lipotoxicity. This article systematically reviews the mechanisms, clinical features, and management strategies of dyslipidemia in diabetes, with a particular focus on lipid metabolism pathways (e.g, cholesterol synthesis) and the therapeutic potential of novel drugs targeting the gut microbiota or inflammation. The primary objective is to provide a detailed analysis of the metabolic mechanisms in diabetes, using lipid metabolism as a framework, and to offer new perspectives for the treatment and prognosis of the disease.

Keywords: diabetes mellitus, dyslipidemia, insulin resistance, oxidative stress, lipotoxicity, cholesterol synthesis

Introduction

Diabetes mellitus (DM), as a chronic metabolic disease, is characterized by insufficient insulin secretion or functional defects, leading to persistent hyperglycemia, and is also accompanied by disorders in lipid and protein metabolism.[1,2] Hyperglycemia, hyperlipidemia, and the excessive accumulation of Advanced glycation end products (AGEs) contribute to the pathological process of DM. In recent years, Type 2 diabetes mellitus (T2DM) has been increasingly diagnosed in younger populations, with its incidence among teenagers rising annually. This trend has drawn significant attention from the medical community. Effective prevention and control of the disease's progression are the keys to its management.[3,4] Long-term hyperglycemia may lead to multiple organ involvement, and patients often experience symptoms in multiple systems. The clinical manifestations include typical symptoms such as polyuria, polyphagia and polydipsia, and may also be accompanied by skin itching and blurred vision. In addition, insulin deficiency or resistance can accelerate fat breakdown and increase blood lipid levels, thereby increasing the risk of cardiovascular diseases.[5,6] Similarly, a high-glycemic environment disrupts the balance between protein synthesis and decomposition, impairing the body's repair and functional maintenance.[7,8] Although existing studies have shown that hypoglycemic drugs (eg, biguanides, sulfonylureas,

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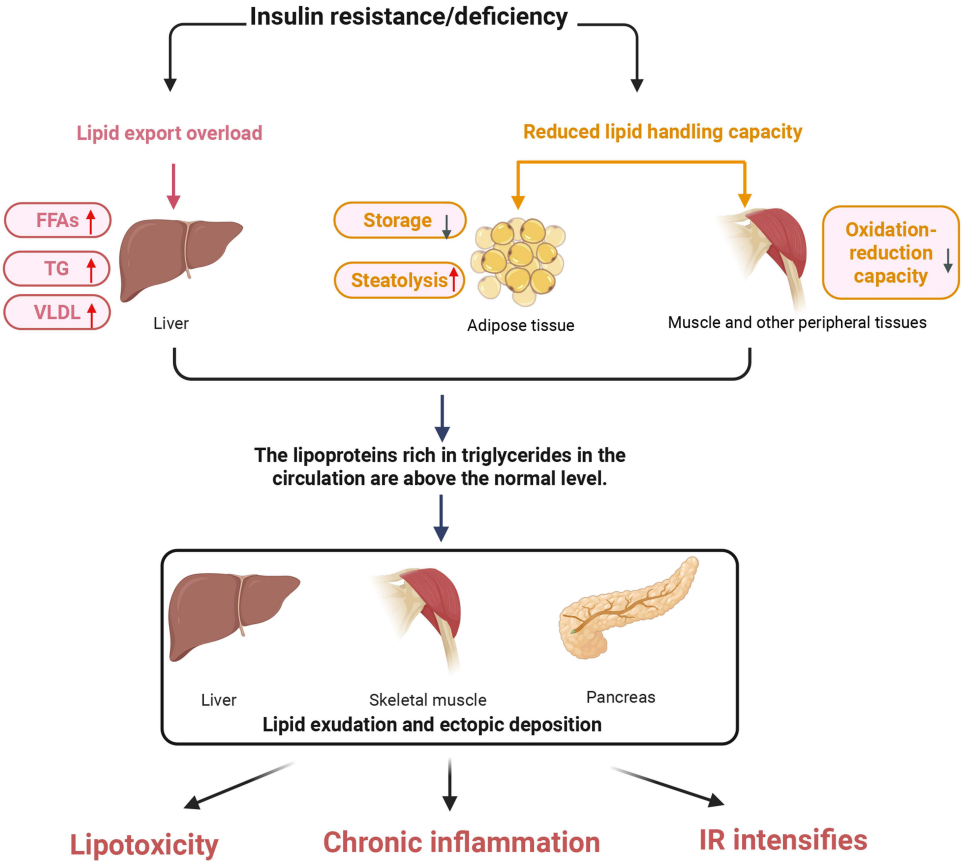
Graphical Abstract



glinides, etc.) have significant therapeutic effects in the treatment of DM, the hastening prevalence of DM and its high risk of complications pose a major challenge to medical researchers.

The lipid metabolism changes in patients with DM persist throughout the entire course of the disease. Lipid output overload and decreased lipid metabolism capacity are the two key mechanisms leading to lipid metabolism disorders. On the one hand, the biosynthesis or intake of lipids is excessive, which overwhelms the body's metabolic capacity. This can be driven by, for instance, increased hepatic lipogenesis or elevated intestinal absorption of exogenous fat. On the other hand, the body's capacity for lipid metabolism is diminished, leading to impaired breakdown, transport, and utilization of lipids. This is often due to dysfunction in key elements such as metabolic enzymes and apolipoproteins; a typical example is the reduced activity of lipoprotein lipase in DM.[9,10] Abnormal lipid metabolism, which is present in nearly all diabetic patients and persists throughout the disease course, is a major driver of DM complications. Furthermore, epidemiological studies show a growing risk of cardiovascular and cerebrovascular diseases attributable to this metabolic abnormality.[11,12] Similarly, abnormal lipid metabolism elevates the risk of microvascular diseases, such as diabetic nephropathy and diabetic peripheral neuropathy.[13,14] Elevated Triglyceride (TG) levels are a common manifestation associated with insulin resistance (IR), lipolysis, and increased hepatic synthesis. Similarly, TG levels constitute an independent risk factor for increased atherosclerosis risk, mediated by mechanisms such as triglyceride-rich lipoproteins (TRLs) and their remnants, inflammation, and endothelial dysfunction. Furthermore, hHigh-Density Lipoprotein Cholesterol (HDL-C), which has anti-atherosclerotic effects, is often reduced, thereby increasing the risk of cardiovascular diseases. Moreover, elevated Low Density Lipoprotein Cholesterol (LDL-C) levels significantly raise the risk of atherosclerosis.[15–17] Abnormal lipid metabolism is a major driver of cardiovascular complications in DM, a fact of

considerable clinical relevance. Epidemiological studies show that vascular lesions start to form in the prediabetic phase or early stages of the disease.[18,19] Furthermore, abnormal lipid metabolism contributes significantly to diabetic microvascular complications, including nephropathy and retinopathy.

Research indicates that effective diabetes management requires a combination of pharmacological treatment with lifestyle interventions, including diet, exercise, and weight control, to alleviate symptoms and enhance quality of life.[20,21] Regulating lipid metabolism is also essential for achieving glycemic control and is a core strategy for preventing serious complications. This review discusses the role of lipid metabolism in the pathophysiology of DM and the development of novel therapeutic strategies targeting lipid disorders. It further explores the mechanisms and treatments related to lipid metabolism in both macrovascular and microvascular complications of DM. A thorough understanding of the role of lipids in DM pathogenesis and complications paves the way for novel drug development and enhances opportunities for early intervention and treatment.

The Molecular Mechanism of Abnormal Lipid Metabolism of Diabetes Mellitus

Core Initiating Factor – Insulin Resistance

Insulin resistance (IR) is a fundamental pathological mechanism in T2DM and is closely associated with obesity. In patients with T2DM, obesity exerts a multi-pathway synergistic effect through lipotoxicity, chronic inflammation, imbalance of adipokines, and dysbiosis of the gut microbiota, leading to impaired insulin signaling and ultimately triggering systemic insulin resistance. These mechanisms are interwoven and mutually amplify each other, forming the core pathological basis for the onset of T2DM. (Figure 1) Physiologically, insulin orchestrates fuel metabolism (glucose and free fatty acids) to meet energy demands during dietary cycles and physical activity.[22] Insulin mediates the transport of substrates into tissues for oxidation and storage via the insulin receptor signaling pathway, which modulates

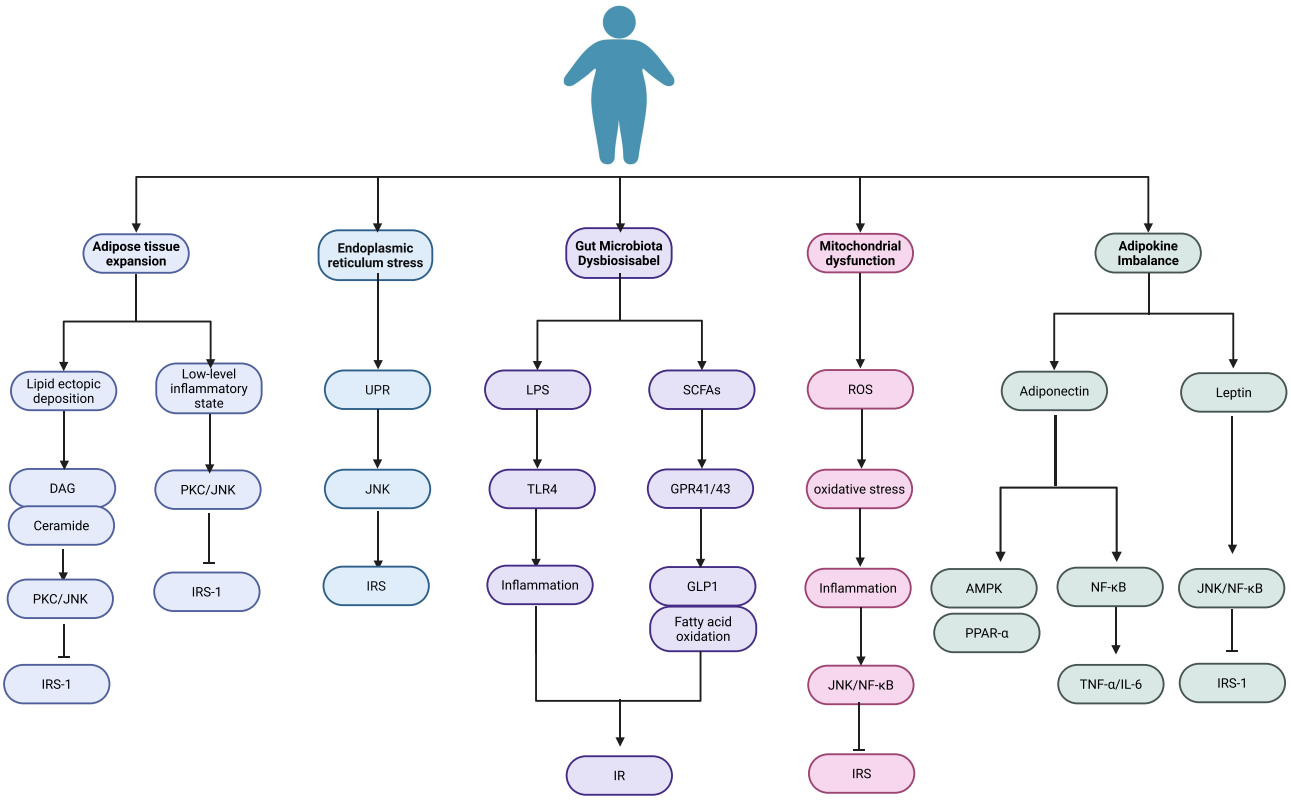


Figure 1 The mechanism of IR as a consequence of obesity in T2DM. Abnormal lipid accumulation, chronic inflammation, imbalance of fat factors, mitochondrial/endoplasmic reticulum dysfunction, and gut microbiota disorder are all key factors contributing to insulin resistance in T2DM. The figures created by BioRender.

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downstream cellular processes.[23] Under normal conditions, insulin suppresses lipolysis (fat breakdown). However, with the onset of IR, this inhibitory effect is impaired. This leads to excessive free fatty acids (FFAs) entering the bloodstream, impairing multiple organ systems via mechanisms including lipotoxicity, oxidative stress, and inflammation. Insulin plays a key role in coordinating glucose uptake and metabolism, particularly in the liver and skeletal muscle. An excess of FFAs entering the liver provides surplus substrate for TG synthesis. This increased lipid flux stimulates hepatic production and secretion of VLDL, ultimately leading to hypertriglyceridemia.[24,25]

Studies have shown that key factors contributing to IR include impaired oxidation of FFAs and ectopic accumulation of triglycerides. Excessive lipid deposits accumulate in tissues such as the liver and pancreas that are not suitable for fat storage. This ectopic lipid deposition further aggravates IR, with hepatic accumulation leading to fatty liver disease and pancreatic accumulation impairing β-cell function.[26,27] Similarly, under normal conditions, insulin stimulates the re-esterification of FFAs into TG within adipocytes. However, IR inhibits glucose metabolism in fat cells. The resultant decrease in 3-Phosphoglyceric acid, a key intermediate, impairs the re-esterification process, thereby reducing triglyceride storage.[28] Secondly, under normal conditions, insulin can inhibit the breakdown of TG in storage by suppressing the rate-limiting enzyme of lipid breakdown, hormone-sensitive lipase (HSL). In the state of IR, the inhibitory effect on fat breakdown weakens. FFAs can activate the TLR4/NF-κB pathway and the NLRP3 inflammatory body, releasing substances such as TNF-α, IL-6, IL-1β, and MCP-1, which further aggravate insulin resistance, endothelial damage, and organ dysfunction, affecting lipid and carbohydrate metabolism, thereby forming a vicious cycle.[29,30]

Toxic Effects of Free Fatty Acids

In the bodies of diabetic patients, excessive FFAs not only serve as an energy source but also act as a "metabolic toxin". They contribute to the pathogenesis and progression of DM by both intensifying IR and directly damaging pancreatic β cells.[31,32] Therefore, reducing FFAs levels and improving lipid metabolism are among the effective measures for the prevention and treatment of DM. Since the proposal of the adipotoxicity theory, disorders of glycolipid metabolism have been recognized as the pathophysiological basis of T2MD and its complications.

The lipotoxicity of FFAs primarily involves their direct toxic effects on pancreatic β cells, which is also the primary reason for defects in insulin secretion. Its mechanism of action is to trigger endoplasmic reticulum stress and oxidative stress, which in turn interferes with insulin biosynthesis and ultimately leads to cellular dysfunction.[33,34] Chronic elevation of circulating FFAs forces pancreatic β-cells to uptake excessive lipids. When the influx of FFAs exceeds mitochondrial oxidative capacity, surplus fatty acids are diverted into alternative synthetic pathways, leading to the accumulation of toxic lipid intermediates, notably ceramides. Ceramide, as a potent bioactive signaling molecule, induces apoptosis through multiple mechanisms such as inhibiting survival signals, activating death signals, and disrupting mitochondrial function.[35] This results in inadequate insulin secretion, a key step in the progression from IR to clinical manifestations of DM, such as hyperglycemia and hyperlipidemia. Notably, when hyperglycemia and hyperlipidemia coexist, their damaging effects on pancreatic β cells are synergistically amplified, thereby exacerbating cellular dysfunction.

Similarly, FFAs also exert detrimental effects on insulin target tissues, such as the liver and skeletal muscle, a mechanism that contributes to the exacerbation of IR. Excessive FFAs influx into muscle cells disrupts the balance between oxidative energy supply and storage, leading to the cytoplasmic accumulation of triglycerides. During this esterification process, toxic intermediates such as ceramides and diacylglycerols are generated.[36] These substances interfere with insulin signaling, thereby impairing glucose uptake and utilization by skeletal muscle cells. This ultimately disrupts glucose homeostasis and contributes to peripheral IR. In summary, by blocking insulin signaling pathways and impairing the response of muscle cells, FFAs and its derivatives prevent the effective regulation of blood glucose.

Similarly, when a large plenty of FFAs enter the liver, they are synthesized into triglycerides. The accumulation of these triglycerides disrupts hepatic lipid metabolism, thereby causing hepatic steatosis and Non-alcoholic fatty liver disease (NAFLD) and thus further aggravating IR in the liver.[37,38] In hepatocytes, diacylglycerol (DAG), an intermediate of triglyceride metabolism, acts as a second messenger to directly activate the ε subtype of protein kinase C (PKCε). The activated PKCε has the ability to promote the phosphorylation of the key threonine residues on the insulin receptor kinase (IRK). This modification interferes with normal insulin signal transduction, leading to dysfunction of the downstream

PI3K-Akt pathway. Consequently, the liver's ability to utilize glucose is impaired and gluconeogenesis cannot be effectively suppressed, ultimately manifesting as hepatic IR.[39,40]

Abnormal Regulation of Key Enzymes in Lipoprotein Metabolism

Diabetic dyslipidemia is characterized by the dysregulation of key enzymes in lipoprotein metabolism, a central pathophysiological feature primarily driven by IR and hyperinsulinemia. Critically involved enzymes include lipoprotein lipase (LPL), hepatic lipase (HL), and 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase).

Insulin is a key regulator of LP activity. During IR, its ability to stimulate LPL in adipose tissue is diminished, resulting in reduced LPL synthesis and activity. Consequently, the hydrolysis of triglycerides in chylomicrons (CM) and VLDL is impaired, prolonging their circulation in the bloodstream and leading to hypertriglyceridemia.[41,42] In DM, hepatic lipase (HL) activity is elevated. Within the hypertriglyceridemic environment, cholesterol esters and triglycerides are exchanged between VLDL and LDL particles, resulting in triglyceride-enriched LDL. The enhanced HL activity then hydrolyzes the triglycerides in these modified LDL particles, thereby altering their properties.[43] HMG-CoA reductase is the rate-limiting enzyme in the cholesterol synthesis pathway and also the target for statin lipid-lowering drugs.[44,45] (Figure 2) A well-established vicious cycle in DM involves the reciprocal aggravation of IR and dysregulated cholesterol metabolism. IR enhances the activity of HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis. This, in turn, promotes aberrant mevalonate pathway sign.[46]

In DM, lipid metabolism disturbances manifest as a coordinated dysfunction of enzymatic systems driven by IR. Elucidating the aberrant regulation of these key enzymes clarifies the pathogenesis of diabetic dyslipidemia and provides a rationale for combination therapy using lipid-lowering agents with distinct mechanisms.

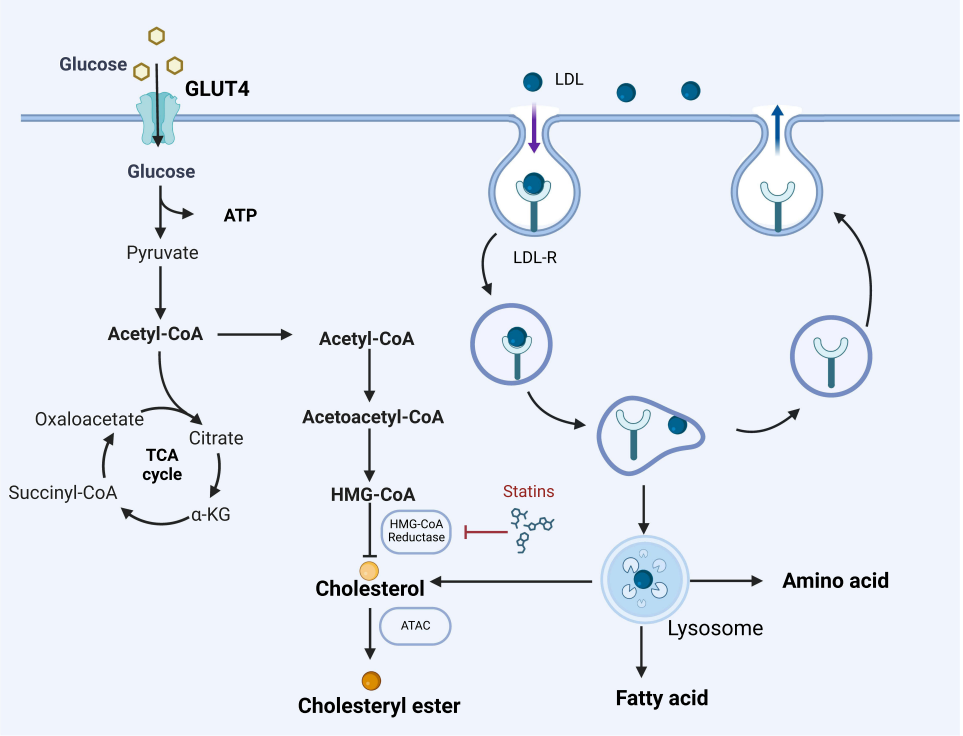

Figure 2 The key localization of HMG-CoA reductase in lipid metabolism of diabetes. Statins can competitively inhibit HMG-CoA reductase, reducing cholesterol production in the liver. At the same time, by upregulating LDL-R, they promote the clearance of LDL in the blood, thereby significantly lowering total cholesterol and LDL levels. The figures created by BioRender.

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AGES Exacerbate Lipid Metabolism Abnormalities

AGEs are defined as a class of harmful compounds resulting from the non-enzymatic glycation of proteins and lipids. The formation of AGEs is an irreversible, non-enzymatic chemical process. Initially, reducing sugars (e.g., glucose) spontaneously react with protein amino groups to form unstable Schiff bases. Subsequently, these bases undergo rearrangement to form more stable Amadori products. Finally, under conditions such as oxidative stress or prolonged exposure, these Amadori products undergo dehydration, cleavage, and cross-linking reactions, transforming into complex and stable AGEs. The hyperglycemic state promotes the pathological accumulation of AGEs by supplying abundant precursors for these reactions.

AGEs interfere with lipid metabolism by directly modifying lipoproteins and altering their function. For instance, they can modify apolipoprotein B on LDL particles.[47] Glycated LDL is poorly recognized by LDL receptors; it is instead readily phagocytosed by macrophages.[48] This process triggers macrophages to phagocytose large amounts of glycated LDL and transform into lipid-laden foam cells, the crucial initial step in atherosclerotic plaque formation.[49] AGEs also promote atherosclerosis by impairing the reverse cholesterol transport capacity of HDL. This occurs when glycated HDL fails to effectively transport cholesterol from other tissues to the liver—a key anti-atherosclerotic function of HDL.[50] AGEs also disrupt lipid metabolism via Receptor for Advanced Glycation End Products (RAGE)-mediated inflammatory and oxidative stress pathways. AGEs, by binding to their receptor RAGE, further activate the NF-κB pathway. This activation promotes the production of numerous pro-inflammatory factors, creating a state of chronic, low-grade inflammation that interferes with insulin signaling, exacerbates IR, and ultimately worsens overall lipid metabolism.[51,52] (Figure 3)

AGEs contribute to abnormal lipid metabolism through multiple pathways. Firstly, the AGE-RAGE interaction stimulates lipolysis, elevating plasma FFAs, which exacerbates IR. Secondly, AGEs induce hepatic VLDL

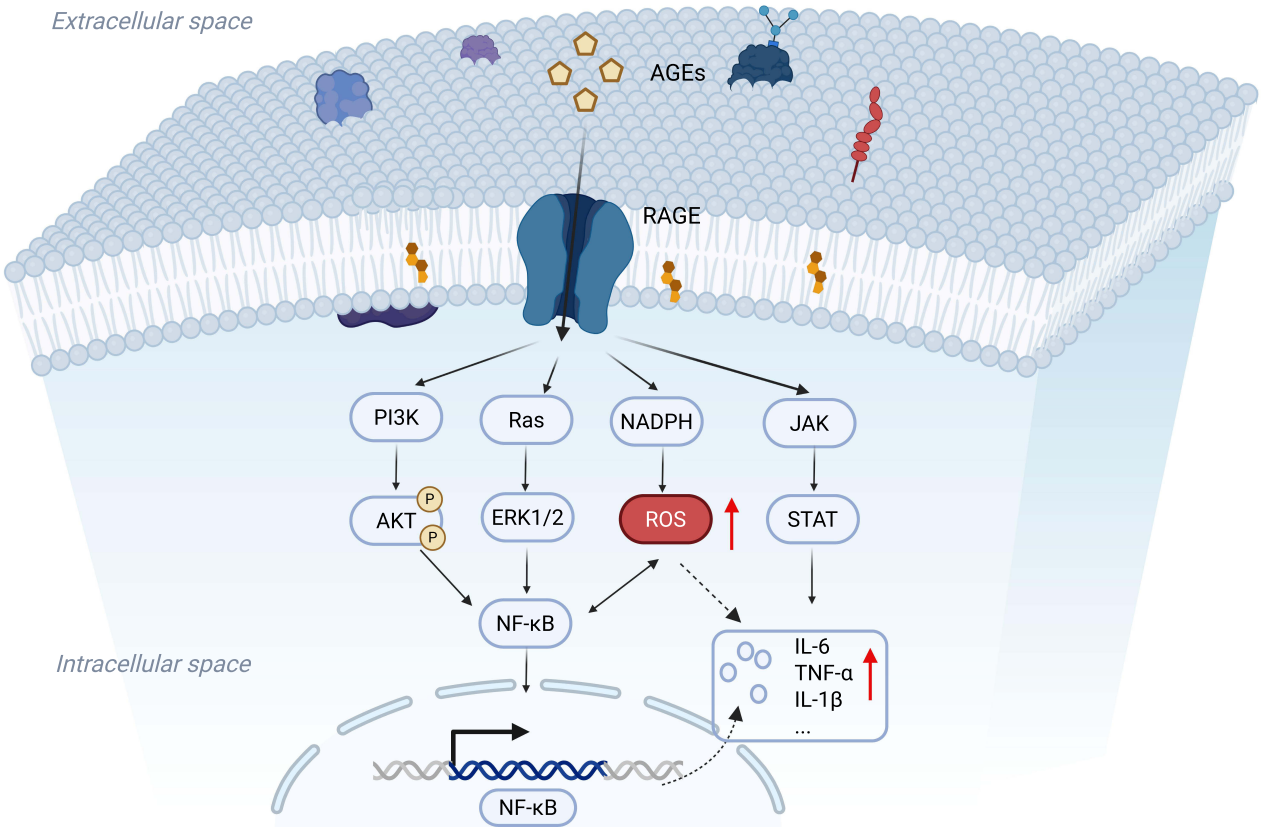

Figure 3 The accumulation of AGEs facilitates the production of inflammatory factors and reactive oxygen species. AGEs can bind to their receptor RAGE, simultaneously releasing and activating NF-κ B. The activated NF-κB enters the cell nucleus, promoting the gene expression of inflammatory factors such as IL-6 and TNF-α. The figures created by BioRender.

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overproduction, leading to hypertriglyceridemia. Furthermore, this resultant dyslipidemia promotes additional AGEs formation, a feedback loop believed to be mediated primarily by enhanced oxidative stress.

Diabetes from the Perspective of Sphingolipid Metabolic Homeostasis

Sphingolipids, which are a type of structural lipids with sphingosine as their backbone, play a significant role in cell membranes and cellular signaling. Among them, ceramides and sphingosine 1-phosphate (S1P) are two critical metabolic molecules. Disorders of sphingolipid metabolism emerge as critical contributors to the development of DM and associated complications, particularly neuropathy. Ceramides are multiple metabolic precursors and hubs. High levels of ceramides can promote IR, inflammation and apoptosis.[53,54] S1P, on the other hand, has the opposite effect of ceramide. It promotes cell proliferation and survival and has anti-inflammatory effects.[55,56] The diabetic state (especially hyperglycemia and elevated FFAs) can disrupt the balance of sphingolipid metabolism through multiple pathways, leading to lipid toxicity, which is specifically manifested as increased ceramide production and relatively reduced levels or functions of sphingosine 1-phosphate.

Sphingolipid metabolism disorders contribute significantly to DM by inhibiting insulin signaling and promoting resistance. Ceramides, for example, impair insulin signaling in muscles and the liver by disrupting pathways like AKT/PKB activation. This reduces cellular insulin sensitivity, prevents effective glucose uptake, and ultimately leads to hyperglycemia.[57] Secondly, diabetic-induced endoplasmic reticulum stress and mitochondrial dysfunction activate sphingolipid synthesis, resulting in ceramide accumulation that exacerbates insulin signaling obstruction, thereby creating a vicious cycle.[58] Furthermore, ceramides contribute to inflammation by activating pathways like NF-κB, which prompts the secretion of inflammatory factors from adipose tissue and further drives IR.

Similarly, long-term complications of DM, such as cardiovascular disease, kidney disease, and retinopathy, are also linked to disruptions in sphingolipid metabolism. In particular, ceramide accumulation in nerves is a direct driver of diabetic neuropathy. Ceramides act not merely as metabolic waste but as potent toxic signaling molecules. By depleting energy, inducing oxidative stress and inflammation, blocking axonal transport, and triggering apoptosis, they directly drive the structural damage and functional loss characteristic of diabetic neuropathy.

Abnormal Lipid Metabolism Under the Influence of Gut Microbiota

The interplay between intestinal microbiota stability and lipid metabolism plays a significant role in the development of DM. The core mechanism is microbiota imbalance. This dysbiosis leads to IR and abnormal lipid metabolism by triggering systemic inflammation, reducing beneficial metabolites, and disrupting bile acid signaling. These metabolic abnormalities then feedback to exacerbate the dysbiosis.

In DM, impairment of the intestinal barrier allows opportunistic pathogenic bacteria to proliferate. Consequently, large amounts of lipopolysaccharide (LPS) from their cell walls translocate the bloodstream, causing metabolic endotoxemia. This condition activates inflammatory pathways like NF-κB, which ultimately leads to systemic chronic low-grade inflammation.[59] Secondly, the production of beneficial short-chain fatty acids (SCFAs) by the gut microbiota, including acetate, propionate, and butyrate, is impaired as a result of the decreased abundance of commensal bacteria. For instance, in addition to being the primary energy source for intestinal epithelial cells, butyrate plays an essential role in preserving the intestinal barrier, a function crucial for overall gut health. Consequently, a deficiency in butyrate can exacerbate intestinal leakage.[60] Similarly, SCFAs also bind to G protein-coupled receptors, which stimulates the secretion of GLP-1 and peptide YY. This leads to increased insulin sensitivity, suppressed appetite, and improved glycolipid metabolism.[61,62] The gut microbiota can also participate in the metabolic transformation of bile acids. Dysbiosis of the microbiota can alter the composition of bile acids. Bile acids function not merely as lipid emulsifiers but also as crucial signaling molecules. They regulate glucose and lipid metabolism primarily by activating the farnesoid X receptor (FXR) and the G protein-coupled bile acid receptor 1 (TGR5).[63,64] (Figure 4) Similarly, dysbiosis leading to abnormal bile acid signaling can also exacerbate IR and lipid metabolism disorders.

Disordered lipid metabolism in DM acts on the gut microbiota and affects microecological homeostasis. It has been demonstrated that high cholesterol and triglyceride levels can drive the expansion of specific bacterial taxa that metabolize these lipids, leading to a shift in microbiota structure. The intestinal microbiota, a key "metabolic organ"

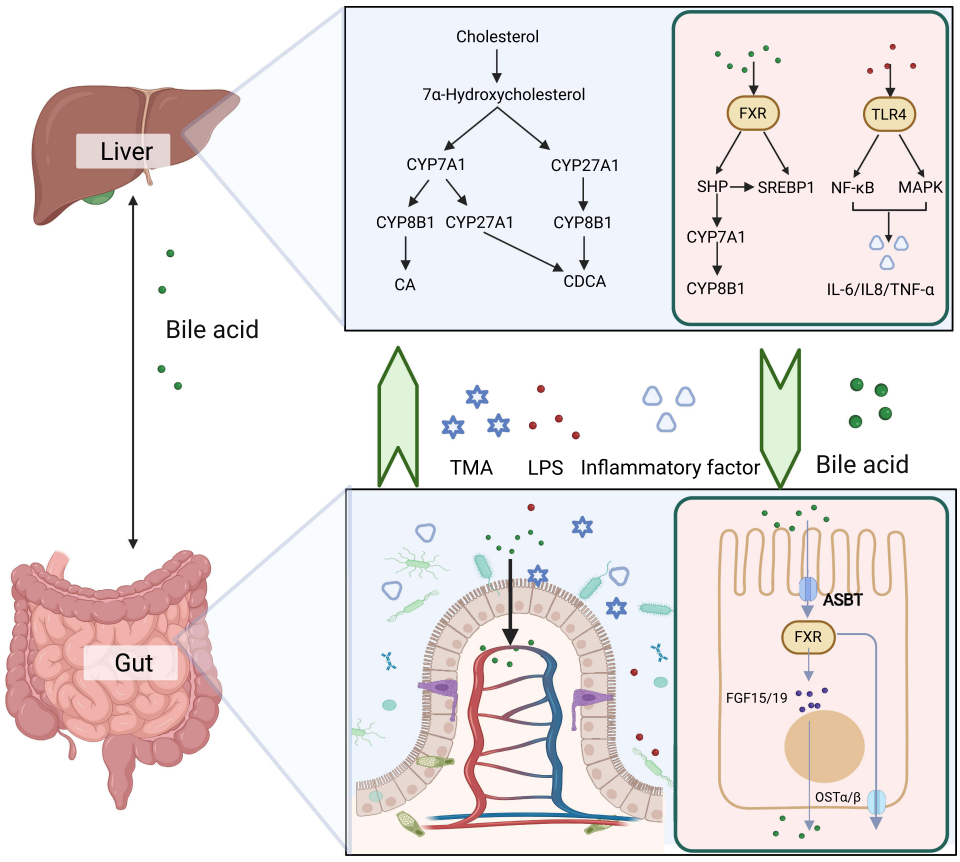

Figure 4 Bile acid metabolism is regulated by the gut microbiota. In diabetes, the disrupted gut microbiota leads to the accumulation of LPS and other metabolites (e.g, TMA). These are transported to the liver via the portal vein, which in turn promotes the production of inflammatory factors. This creates a pro-inflammatory environment that exacerbates lipid metabolism disorders. The figures created by BioRender.

that regulates host glucose and lipid metabolism, has emerged as a promising new therapeutic target. This approach aims to combat DM and its lipid-related complications by rectifying microbial dysbiosis and reestablishing a healthy gut ecosystem.

Clinical Features of Abnormal Lipid Metabolism in DM

New Insights into Metabolic Disorders from the Perspective of Lipidomics

The classic lipid profile in DM is characterized by elevated TG and reduced HDL-C. However, insights from lipidomics indicate that the underlying metabolic dysregulation is much more intricate, encompassing a wider array of lipid species and pathways.

Diacylglycerols (DAGs) and TGs play a central role in IR. DAGs, the precursors to TGs, accumulate in insulin-sensitive tissues and activate specific PKC isoforms, thereby impairing insulin signaling. Additionally, in DM, both the increased level and altered fatty acid profile of TGs further promote IR. Sphingomyelin, as an important type of signaling lipid, plays a key role in the pathogenesis of DM. The focus is mainly on two types of signaling lipids: ceramides and sphingosine 1-phosphate. Ceramides, a class of signaling molecules that have garnered significant attention, promote IR and β-cell failure primarily by inhibiting the activation of insulin receptor substrate-1 and stimulating inflammatory responses.[65] Lipidomic studies have demonstrated that ceramides are more accurate biomarkers for predicting DM risk compared to conventional indicators. Ceramide accumulation typically occurs in the early stages of metabolic dysregulation. Even before the onset of hyperglycemia, FFAs spillover and increased ceramide synthesis begin to impair insulin signaling pathways, leading to insulin resistance.[66] Similarly, as the main components of cell membranes, phospholipids modulate membrane fluidity and insulin receptor function. In diabetic patients, an increased ratio of phosphatidylcholine

to phosphatidylethanolamine is commonly observed. Furthermore, certain phospholipid metabolic intermediates, such as lysophospholipids, are implicated in insulin and inflammatory signaling. For example, the enzyme LPCAT3 has been shown to influence insulin receptor phosphorylation.[67]

Lipid metabolic dysfunction is a key driver of DM pathogenesis. Driven by overnutrition and obesity, dysfunctional adipose tissue releases excessive FFAs and inflammatory factors. The deposition of these lipids in non-adipose organs generates toxic species (e.g., ceramides, diacylglycerols), promoting IR and β-cell damage. The resulting decline in insulin secretion perpetuates a vicious cycle of metabolic deterioration.

Clinical Manifestations of Lipid Metabolism Disorders in DM

The clinical manifestations of diabetic dyslipidemia are characteristic yet often insidious. In the early phase, abnormalities are usually confined to laboratory findings, while symptoms are most commonly associated with vascular complications. The characteristic pattern of this dyslipidemia includes elevated triglycerides, decreased HDL-C, and qualitative changes in LDL-C particles.[68]

Lipid metabolism disorders themselves are typically asymptomatic. Their clinical significance lies primarily in accelerating atherosclerotic cardiovascular disease (ASCVD) and promoting the microvascular complications of DM. The most dangerous consequence of diabetic dyslipidemia is the acceleration of macrovascular complications, including coronary artery disease (manifesting as angina, heart failure, etc.), cerebrovascular disease (eg, cerebral ischemia or infarction), and peripheral artery disease (stenosis or occlusion of lower-extremity arteries). (Figure 5) The acceleration of microvascular complications represents another major clinical manifestation. Dyslipidemia in DM drives a spectrum of complications through lipid deposition in end-organs. Renal involvement accelerates glomerular and tubular damage, leading to proteinuria and renal impairment. Retinal accumulation worsens retinopathy, increasing blindness risk. Notably, very high triglycerides may cause acute pancreatitis. Since its first sign is often a life-threatening event, dyslipidemia must be proactively managed with regular screening and intensive intervention in all diabetic patients.

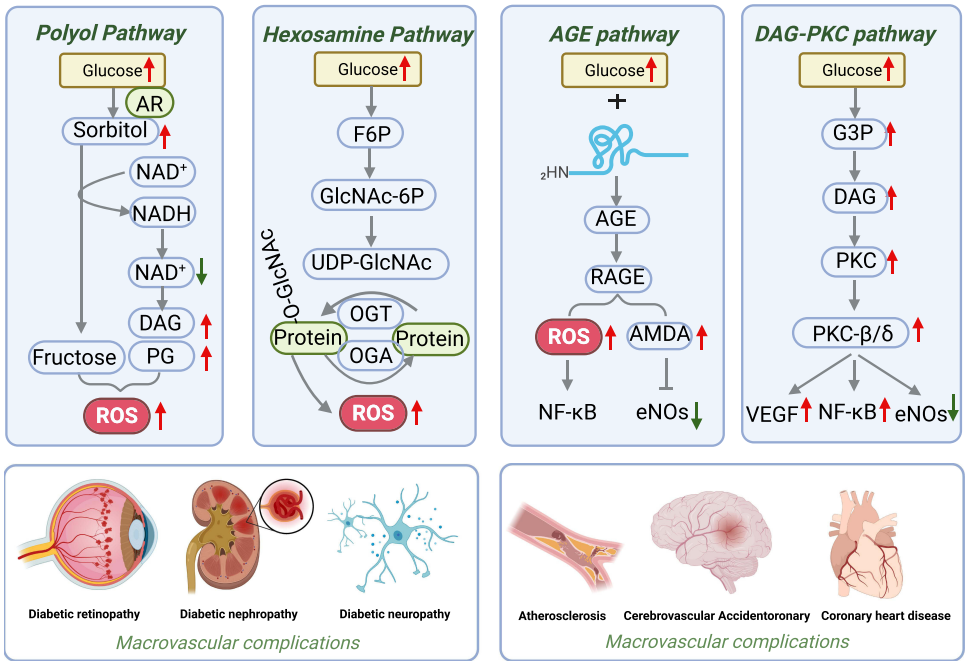

Figure 5 Under long-term hyperglycemic conditions, there are common molecular mechanism pathways for microscopic vascular diseases (such as retinopathy, nephropathy, and neuropathy) and macroscopic vascular diseases (such as atherosclerosis, coronary heart disease, and stroke). These pathways are mainly driven by persistent hyperglycemia and interact synergistic through key pathways such as the Polyol Pathway, Hexosamine Pathway, AGE Pathway, and DAG-PKC Pathway. The figures created by BioRender.

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Abnormal Lipid Metabolism in Diabetic Complications

Macrovascular Complications

Coronary Artery Disease

Patients with DM face a 2- to 4-fold increased risk of coronary heart disease, which often manifests at a younger age and follows a more aggressive course than in non-diabetic individuals. Diabetic patients have an increased risk of mortality after myocardial infarction, along with a higher incidence of serious complications like heart failure, compared to their non-diabetic counterparts.[69,70] Long-term hyperglycemia and IR damage the vascular endothelium, the innermost layer of blood vessels. This endothelial injury, which constitutes endothelial dysfunction, promotes lipid deposition and inflammation, thereby accelerating the formation of atherosclerotic plaques.[71]

Abnormalities in lipid metabolism are key drivers of atherosclerosis. These dysfunctional lipoproteins are more likely to infiltrate and accumulate within damaged vessel walls, forming foam cells that constitute the plaque core.[72] Similarly, abnormal lipids can directly impair key functions of vascular endothelial cells, including their vasodilatory, anti-inflammatory, and anticoagulant properties. This disruption facilitates the formation of atherosclerotic plaques. Lipid disorders and IR act in concert to promote a pro-thrombotic state by enhancing platelet aggregation, increasing the activity of coagulation factors, and suppressing the fibrinolytic system. The rupture of an unstable atherosclerotic plaque under these conditions can rapidly lead to thrombus formation, resulting in complete coronary artery occlusion and acute myocardial infarction.

Cerebrovascular Disease

Diabetic cerebrovascular disease manifests primarily as stroke, a leading cause of disability and mortality in diabetic patients. Stroke in diabetic patients represents the cerebral manifestation of systemic atherosclerosis, accelerated by DM. The underlying pathological processes involve several key mechanisms. Firstly, disordered lipid metabolism promotes endothelial damage, leading to the accumulation of atherosclerotic plaques in the carotid and intracranial arteries.[73] These plaques cause vascular stenosis or occlusion. Secondly, a chronic hypercoagulable state coupled with enhanced platelet activity in diabetics means that any plaque rupture readily triggers thrombosis, which can rapidly occlude cerebral vessels and cause an ischemic stroke.[74] Furthermore, DM impairs the autoregulatory function of cerebral vasculature, compromising the ability to maintain stable cerebral blood flow during blood pressure fluctuations, thereby increasing the risk of both ischemic and hemorrhagic events. Finally, persistent inflammatory responses and oxidative stress significantly contribute to ongoing vascular injury and plaque destabilization.

Hyperglycemia and dyslipidemia act synergistically to induce endothelial dysfunction, initiating and sustaining a state of chronic inflammation and oxidative stress. This pathological milieu fosters the initiation and progression of atherosclerosis. In DM, the characteristic lipid profile further promotes the formation of vulnerable plaques, which carry a high risk of rupture and can directly precipitate acute cerebrovascular events (eg, cerebral infarction).[75] Optimal glycemic control and management of dyslipidemia are crucial for reducing the risk of cerebrovascular disease in patients with diabetes.

Peripheral Arterial Disease

A close and significant connection exists between peripheral artery disease (PAD) and DM. As a major independent risk factor, DM significantly accelerates the progression of atherosclerosis. Diabetic patients have a risk of PAD that is several times higher than that of non-diabetic patients. Moreover, their disease onset is earlier, progresses more rapidly, and is more severe.[76] PAD serves as a window to systemic atherosclerosis. Once diabetic patients develop PAD, their risk of myocardial infarction, stroke, and cardiovascular death increases exponentially. Therefore, it is crucial to conduct routine PAD screening for diabetic patients. Blood glucose, blood pressure, and lipid levels should be strictly controlled to delay disease progression. Concurrently, in patients with established PAD, active antiplatelet therapy, revascularization, and professional foot care are essential to prevent amputation and cardiovascular events.[77,78]

PAD and abnormal lipid metabolism interact to create a vicious cycle, which significantly accelerates atherosclerosis and increases the risk of amputation and cardiovascular events. Factors such as IR not only cause a characteristic atherosclerotic lipoprotein profile but also act synergistically to damage blood vessels via multiple

mechanisms. Structurally modified LDL particles are more likely to infiltrate the vessel wall and become oxidized, thereby promoting plaque formation.[79] Lipid abnormalities, specifically high TG and low HDL-C, compromise the vascular protective and repair mechanisms. A hyperglycemic environment significantly exacerbates oxidative stress by elevating ROS derived from intracellular glucose metabolism, acting synergistically with ROS generated from mitochondrial β-oxidation overload induced by excessive free fatty acids (FFAs). This heightened oxidative stress activates the NF-κB inflammatory pathway, prompting vascular endothelial cells to express adhesion molecules and secrete pro-inflammatory cytokines, thereby establishing a chronic low-grade inflammatory state. Ultimately, this cascade results in endothelial dysfunction and vascular microenvironment remodeling, directly driving the initiation and progression of atherosclerosis.

Microvascular Complication

Diabetic Retinopathy

Diabetic retinopathy is one of the most common and serious microvascular complications of DM. Hyperglycemia causes microvascular damage in the retina, with key histopathological features including pericyte loss, endothelial cell damage, and basement membrane thickening.[80,81] Similarly, overactivation of the polyol pathway, heightened oxidative stress, and resultant cellular damage are also key mechanisms contributing to the development of diabetic retinopathy.[82] AGEs induce oxidative stress and inflammation, thereby exacerbating vascular damage.[83] Furthermore, in a state of hyperglycemia, the body tends to overproduce vascular endothelial growth factor (VEGF), which promotes the pathological growth of neovascularization in the retina.[84,85]

Changes in lipoprotein function are a key factor in the development and progression of diabetic retinopathy. Specifically, IR causes an excessive accumulation of FFA in the retina. This accumulation activates signaling pathways such as TLR4/NF-κB, creating a chronic inflammatory environment that damages blood vessels.[86,87] Secondly, in a high-glucose environment, the protective effect of high-density lipoprotein on the retina will be inhibited. The decline in its cholesterol reverse transport and antioxidant capacity compromises the retina's defense. Subsequently, leaked lipids and lipoproteins (primarily LDL) deposit within the retina, forming the typical pathological hallmark of "hard exudates" and leading to abnormal lipid accumulation.[88]

Diabetic Nephropathy

Diabetic nephropathy (DN) is a serious and common microvascular complication of DM and a leading cause of end-stage renal disease. Research has found that the onset of diabetic nephropathy involves an integrated perspective of multiple mechanisms, including the combined effects of lipid metabolism disorders, inflammatory responses, oxidative stress, genetic and epigenetic factors, etc.[89,90] The treatment strategy for diabetic nephropathy has evolved from a sole focus on glycemic control to a multimodal approach. Emerging therapeutic agents, such as SGLT2 inhibitors and non-steroidal MRAs, have demonstrated significant benefits in preserving renal function, making early multi-drug combination therapy a new standard of care.[91,92]

Diabetic nephropathy and disordered lipid metabolism influence each other closely, with the latter being a key driver of the disease's onset and progression. Lipid metabolism disorders primarily damage the kidneys through mechanisms such as lipotoxicity, oxidative stress, and inflammation, which ultimately affect renal hemodynamics. Elevated blood lipids, particularly high levels of triglycerides and FFA, can lead to lipid accumulation in renal intrinsic cells, especially in lipid-sensitive podocytes.[93] This accumulation impairs podocyte function and triggers apoptosis, resulting in disruption of the glomerular filtration barrier and subsequent proteinuria.[94,95] Similarly, the abnormal accumulation of triglycerides and FFAs within renal cells can trigger oxidative stress and inflammation. This creates a vicious cycle: the ensuing inflammatory response exacerbates IR, which in turn worsens the lipid metabolism disorder, leading to progressive kidney damage.[96] Likewise, obesity and lipid metabolism disorders can induce a state of prolonged hyperfiltration and hyperperfusion in the kidneys, particularly the glomeruli. This forces the renal filtration system to work under chronic overload, which accelerates sclerosis and functional deterioration.

Diabetic Neuropathy

Long-term uncontrolled hyperglycemia is the primary cause of diabetic neuropathy. It damages nerves throughout the body, particularly peripheral nerves, primarily through the following mechanisms: First, hyperglycemia activates the polyol pathway, leading to the conversion and accumulation of sorbitol within nerve cells. This process directly interferes with nerve function and leads to damage.[97,98] Secondly, high blood glucose triggers oxidative stress, generating a large number of free radicals that directly attack nerve cells.[99] In addition, elevated blood glucose can lead to the formation of AGEs by binding to proteins and other molecules. These compounds accumulate on nerve fibers and blood vessel walls, directly damaging neuronal structure and function.[100] Furthermore, hyperglycemia critically damages the microvasculature surrounding nerves. This damage manifests as thickened vessel walls and narrowed lumens, which impair blood flow. Since neural tissue, like all tissues, relies on adequate blood perfusion for oxygen and nutrients, this chronic ischemia leads to nerve necrosis and functional loss. These pathways collectively drive the pathogenesis of diabetic neuropathy.

Lipid metabolism disorder is an underlying driver, rather than a mere bystander, in diabetic neuropathy, directly implicated in its development and progression. Its damage to neural structure and function is mediated by mechanisms such as neurotoxicity, microvascular damage, sphingolipid abnormalities, and the accumulation of cytotoxic lipids.[101,102] First, the intracellular accumulation of toxic lipids induces oxidative stress, causing nerve cell death and inflammation. Second, associated microvascular damage leads to neural ischemia and hypoxia, impairing function and repair. Third, disrupted lipid homeostasis in Schwann cells damages the myelin sheath, critically compromising nerve signal conduction. Fourth, the accumulation of specific lipids, notably ceramide, exerts direct neurotoxicity and disrupts protective lipid environments.

Prevention and Control Strategies and Future Prospects

Lifestyle Intervention

Lifestyle intervention is the preferred strategy for managing diabetic dyslipidemia: controlling total calorie intake and maintaining a healthy weight. Weight loss can also improve the levels of triglycerides and LDL-C.[103] Similarly, the proportion of carbohydrate intake should be optimized, and excessive intake of refined carbohydrates and added sugars should be avoided to reduce hepatic triglyceride accumulation and prevent hypertriglyceridemia. At the same time, improving the diet structure by emphasizing dietary fiber and low-glycemic-index foods can help stabilize blood glucose and reduce lipid synthesis.[104,105] Furthermore, increasing the intake of beneficial fats (eg, unsaturated fatty acids) and reducing saturated and trans fatty acids is recommended.

Exercise therapy is equally important. Regular exercise improves insulin sensitivity and promotes the utilisation of glucose and fatty acids by muscle tissue. Therefore, patients with DM should engage in regular aerobic exercise, combined with appropriate strength training, to boost their overall metabolic rate and reduce triglyceride levels.[106,107] Similarly, adopting a healthier lifestyle—such as quitting smoking and drinking, ensuring adequate sleep, and managing stress—is highly beneficial for controlling DM and its complications. These measures work by lowering corticosteroid levels, which in turn helps to slow down IR and correct lipid metabolism disorders.

Drug Treatment Strategies

The management of diabetic dyslipidemia has evolved from a singular focus on lipid-lowering to a comprehensive strategy aimed at reducing cardiovascular risk. This approach must be individualized according to the patient's specific lipid abnormalities and overall risk profile. Statins, which inhibit HMG-CoA reductase to reduce cholesterol synthesis and significantly lower LDL-C levels, remain the cornerstone of drug therapy.[108,109] Experimental studies have confirmed that statins significantly reduce the risk of cardiovascular events in diabetic patients, with additional pleiotropic effects such as anti-inflammation and plaque stabilization.[110,111] Fibrate drugs lower blood lipids by activating the PPAR-α receptor. This mechanism accelerates the breakdown of lipoproteins and reduces their synthesis in the liver by enhancing lipoprotein lipase activity. They are particularly effective in treating patients with severe hypertriglyceridemia.[112,113] For diabetic patients who remain at high cardiovascular risk with moderately elevated triglycerides despite statin therapy,

prescription-grade omega-3 fatty acids are the preferred add-on therapy. These drugs can significantly reduce triglyceride levels and lower the risk of cardiovascular events.[114–116] When LDL-C does not reach the target level with statin monotherapy, a combination therapy strategy should be initiated. The preferred agent to add is ezetimibe, which enhances the lipid-lowering effect by inhibiting intestinal cholesterol absorption and has a favorable safety profile.[117,118] For extremely high-risk patients, PCSK9 inhibitors can be added to further reduce LDL-C levels. They work by blocking the PCSK9 protein, which significantly enhances the liver's ability to clear LDL-C, forming an intensive lipid-lowering strategy.[119,120] Modern hypoglycemic drugs, such as SGLT2 inhibitors (eg, Enavogliflozin) and GLP-1 receptor agonists (eg, liraglutide), have demonstrated benefits beyond glycemic control, including positive effects on cardiovascular health, blood pressure, and body weight.[121,122]

Novel Therapeutic Targets and Future Directions

The pursuit of novel therapeutic targets for abnormal lipid metabolism in DM is a major research focus. The objective has shifted from merely reducing lipid parameters to fundamentally correcting lipotoxicity and restoring metabolic homeostasis. (Table 1) Accordingly, research is transitioning from drugs like statins and fibrates to investigating specific pathogenic molecules, such as ceramides. For instance, drugs designed to inhibit ceramide or modulate the sphingosine-1-phosphate pathway aim to precisely target the key lipid molecules that cause IR and nerve damage.[123,124] Secondly, a paradigm shift is occurring from targeted regulation to comprehensive metabolic remodeling. The therapeutic objective is to reprogram the organism's metabolic state by intervening at fundamental levels of signaling and transcriptional control. Consequently, the development of highly potent and selective AMPK agonists is regarded as a pivotal strategy for ameliorating the overall metabolic disturbances in DM.[125,126] Meanwhile, the new generation of PPARα/δ/γ pan-agonists is designed to more holistically integrate glucose, lipid, and energy metabolism. These agents enhance insulin sensitivity and promote fatty acid oxidation, yet they are associated with a lower incidence of side effects—such as edema and weight gain—commonly seen with traditional therapies.[127,128] Moreover, the pathological interplay between disordered lipid metabolism and chronic inflammation has prompted the exploration of novel anti-inflammatory therapeutics. The research focus lies in inhibiting specific inflammatory pathways induced by lipotoxicity, exemplified by the development of NLRP3 inflammasome inhibitors or CCR2 antagonists. This approach enables the precise blockade of abnormal inflammatory responses in neural and other tissues, circumventing the risks inherent to conventional, non-specific immunosuppression.[129–131] Additionally, counteracting organelle dysfunction caused by lipotoxicity has emerged as a key focus. For example, drugs like PGC-1α agonists aim to combat oxidative stress by boosting mitochondrial biogenesis and improving their quality control.[132] Secondly, given that lipotoxicity compromises cellular autophagy, researchers are investigating the safe pharmacological induction of autophagy to aid nerve cells in clearing accumulated toxic lipids and damaged components. Finally, pioneering research is exploring disruptive technologies through cutting-edge approaches. Examples include gene therapy (using viral vectors for long-term metabolic regulation) and microbiome intervention (modulating gut flora to improve systemic metabolism). Ultimately, drug development for diabetic dyslipidemia is creating a multi-level, precision treatment network designed to reverse the pathology at its source and offer patients safer, more efficient therapies.

Table 1 Novel Therapeutic Targets for Abnormal Lipid Metabolism in Diabetes Mellitus

Target	Mechanism of Action
ALKBH5	Stabilize the mRNA of glucagon receptor (GCGR) and maintain the homeostasis of glucose metabolism.[133]
PPAR	Regulate fatty acid oxidation, lipoprotein metabolism and anti-inflammatory responses.[134,135]
EGFR	The ligand of EGFR, EPigen, can improve abnormal lipid metabolism by regulating the energy metabolism of adipocytes[136]
ANGPTL3	Inhibit the activity of lipoprotein lipase and regulate the metabolism of very low-density lipoprotein[137]
FGF21	Regulate lipid and glucose metabolism, increase insulin sensitivity, promote fatty acid oxidation and energy consumption.[138]
APOC3	Regulate triglyceride metabolism.[139]
CETP	Regulate cholesterol ester transfer and maintain lipid balance.[140]
PCSK9	By lowering LDL receptors and reducing cholesterol clearance, it leads to an increase in blood LDL-C.[141]

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Table 2 Several Active Ingredients Developed from Herbs are Used to Improve Lipid Metabolism Abnormalities in Diabetes Mellitus

Active Ingredients	Source	Research Phase
Tanshinone IIA	Salvia miltiorrhiza	Computer-aided design/Preclinical study
BA-5	Scutellaria baicalensis	Preclinical study
C60	Curcuma longa	Computer-aided design/Preclinical study /Clinical
Puerarin	Pueraria lobata	Preclinical study
LBE-1	Coptis chinensis	Preclinical study /Clinical

New Drug Development Strategies Based on Active Ingredients

Recently, chemical components isolated from various herbs have been found to in-tervene in the progression of DM through multiple pathways and have shown significant therapeutic effects. (Table 2) The polysaccharide components in herbs can regulate liver glycogen synthesis and decomposition by protecting pancreatic islet cells. For instance, Astragalus polysaccharides can alleviate the symptoms of DM by improving disorders of glycolipid metabolism and intestinal inflammatory states, and by inhibiting the growth of opportunistic pathogenic bacteria.[142,143] Similarly, saponin components such as ginsenosides and monk fruit saponins can improve insulin sensitivity and alleviate DM symptoms by regulating insulin secretion. Ginsenoside Re can exert anti-diabetic effects by activating AMPK signaling and reducing oxidative stress responses.[144] Berberine, a typical alkaloid component, has a significant effect on improving DM. It can reduce the levels of TG and LDL-C by activating the AMPK signaling pathway. And as the most thoroughly studied natural lipid-regulating component, it has demonstrated beneficial vascular protective effects and has been applied in the adjuvant treatment of DM and its complications (such as kidney disease).

Herbs indirectly improve lipid metabolism in DM by regulating gut microbiota. The main manifestation is to regulate the structure of the gut microbiota. The active ingredients in the herbs can selectively promote the proliferation of beneficial bacteria and inhibit the reproduction of opportunistic pathogenic bacteria, further enhancing the stability of the intestinal flora ecological niche.[145,146] Similarly, under the condition of DM, the imbalance of gut microbiota often leads to endotoxins such as lipopolysaccharides and LPS entering the bloodstream, triggering chronic low-grade inflammation and subsequently interfering with lipid metabolism. For instance, wolfberry and mulberry leaves can enhance the expression of tight junction proteins, reduce intestinal permeability, maintain the integrity of the intestinal barrier, alleviate systemic inflammation, and improve lipid metabolism disorders.[147,148] Plant active ingredients can also improve lipid metabolism disorders in DM by regulating bile acids and controlling the generation of short-chain fatty acids.

The active ingredients in herbs are a huge treasure trove for the development of new DM treatment drugs. Compared with chemical single-target drugs, they have their unique advantages: on the one hand, they focus more on overall regulation, aiming to re-store the metabolic balance of the body rather than just reducing a single indicator. On the other hand, this overall regulatory pattern can also reduce side effects and delay the development of drug resistance.

Limitations and Challenges in Lipid Metabolism Research

Although significant progress has been made in research on lipid metabolism in DM, this field still faces numerous deep-seated challenges. Firstly, the complexity and heterogeneity of the mechanisms underlying lipid metabolism, along with the vast diversity of lipid species, pose significant obstacles. Unlike traditional research, which primarily focused on indicators like total cholesterol, triglycerides, LDL-C, and HDL-C, modern lipidomics has revealed that different lipid species can exert distinct or even opposing biological functions. Consequently, determining the critical localization and role of specific lipid molecules within the pathological context of DM remains a major challenge. Currently, research on lipid metabolism lacks standardized functional assays that are easily translatable to the clinic. A major challenge stems from the tissue specificity and spatiotemporal dynamics of DM, which lead to significant variations in lipid metabolic pathways across different target organs. Directly obtaining tissue samples (e.g., from the pancreas or retina) for analysis is often impractical. As a result, most studies rely on blood tests, which only reflect systemic averages and cannot accurately capture the lipid metabolic profile within local lesion sites. Secondly, there are significant physiological

differences between species used in research. Metabolic rates, diets, and other factors differ substantially between animal models and humans. Whereas the development of human T2DM is a slow process that unfolds over years or even decades—closely linked to lifestyle factors like a high-fat, high-sugar diet and physical inactivity—animal models induced rapidly by genetic or dietary means may not fully recapitulate this complex pathophysiology. This limitation may explain the frequent failure of preclinical findings in human clinical trials. The lack of specific targets and drugs is also a major problem. Although statins and fibrates can effectively lower blood lipid levels, their mechanisms of action are broad and lack specificity; consequently, they do not address the distinct pathogenic lipid pathways implicated in DM. Therefore, developing agents that can precisely counteract DM-related lipotoxicity—for example, by specifically reducing ceramide synthesis or improving HDL function—presents substantial challenges, not least because of potential safety concerns. Substantial interindividual variation among diabetic patients means that the risk of complications can differ significantly even among individuals with similar blood glucose and lipid levels. A central challenge for precision medicine, therefore, is to identify those patients whose disease progression is primarily driven by lipid metabolism disorders, so as to guide more intensive lipid-lowering therapy.

Conclusion

Abnormal lipid metabolism is a central mechanism in the pathophysiology of DM. This dysregulation encompasses not only abnormalities in traditional lipid parameters but also alterations in lipoprotein structure, composition, and functionality. IR and dysregulated lipolysis increase circulating FFAs, triggering lipotoxicity that drives the onset and progression of DM and its complications. Recent multi-omics studies have offered new insights into these processes, leading to the discovery of numerous lipid biomarkers (e.g., ceramides, specific phospholipids) with diagnostic and therapeutic potential. These findings provide deeper insights into the underlying mechanisms and identify novel targets for intervention. Consequently, management requires a comprehensive, individualized strategy including lifestyle and pharmacological therapy. Moving forward, research should focus on developing therapies targeting specific lipid pathways and on creating individualized strategies based on lipidomic profiles to more effectively prevent and manage DM and its complications.

Abbreviations

AGEs, Advanced glycation end products; AKT, Protein Kinase B; AMPK, Adenosine 5′-monophosphate (AMP)-activated protein kinase; ASCVD, Atherosclerotic cardiovascular disease; CCR2, CC Chemokine Receptor 2; CM, Chylomicrons; DAG, Diacylglycerol; DM, diabetes mellitus; DN, Diabetic nephropathy; FFAs, Free fatty acids; FXR, Farnesoid X Receptor; GLP-1, Glucagon-like peptide-1; HDL-C, High density lipoprotein cholesterol; HL, Hepatic lipase; HMG-CoA, 3-Hydroxy-3-methylglutaryl-CoA; HSL, Hormone-sensitive lipase; IL-6, Interleukin-6; IR, Insulin resistance; IRK, Insulin receptor kinase; LDL-C, Low-Density Lipoprotein Cholesterol; LPCAT3, Lysophosphatidylcholine acyltransferases; LPL, Lipoprteinlipase; LPS, Lipopolysaccharides; MRAs, Mineralocorticoid Receptor Antagonist; NAFLD, Non-alcoholic fatty liver disease; NF-κB, Nuclear factor kappa-B; NLRP3, NOD-like receptor thermal protein domain associated protein 3; PAD, Peripheral artery disease; PCSK9, Proprotein Convertase Subtilisin/Kexin Type 9; PGC-1α, Peroxisome proliIerators-activated receptor γ coactivator l alpha; PI3K, Phosphatidyqinositol-3 kinase; PKC, Protein kinase C; PPAR, Peroxisome proliferators-activated receptors; RAGE, Receptor for Advanced Glycation End Products; S1P, Sphingosine 1-phosphate; SCFAs, Short-chain fatty acid; SGLT2, Sodium-dependent glucose transporters; T2MD, Type 2 diabetes mellitus; TG, Triglyceride; TGR5, G protein-coupled bile acid receptor 1; TLR4, Toll Like Receptor 4; TNF-α, Tumor necrosis factor-α; VEGF, Vascular endothelial growth factor; VLDL, Very low density lipoprotein.

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Disclosure

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