

## REVIEW

# Associations Among Microvascular Dysfunction, Fatty Acid Metabolism, and Diabetes

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## Abstract

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels resulting from impaired insulin secretion or insulin resistance. Diabetes poses a major global health concern, because of its increasing prevalence and substantial morbidity and mortality. This review explores the relationships between altered fatty acid metabolism and microcirculatory impairments in diabetes. Dysregulation of fatty acid metabolism in diabetes leads to changes in fatty acid profiles, abnormal lipid accumulation, and increased oxidative stress. These changes contribute to microvascular dysfunction through mechanisms such as endothelial dysfunction, impaired nitric oxide availability, inflammation, and oxidative damage. Understanding this intricate interplay is essential for identifying novel therapeutic strategies to alleviate vascular complications in diabetes. By targeting specific pathways involved in fatty acid metabolism and microvascular dysfunction, interventions can be developed to improve patient outcomes. This review is aimed at contributing to future research and the development of effective strategies for preventing and managing diabetes-associated microcirculatory impairments, to ultimately enhance the quality of life for people living with diabetes.

**Keywords:** Diabetes mellitus; Microcirculatory impairments; Endothelial dysfunction; Vascular complications; Therapeutic interventions

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## Introduction

Currently, the worldwide prevalence of diabetes in adults is approximately 382 million, and this number is anticipated to surge to 592 million by the year 2035 [1]. This alarming escalation in prevalence, accompanied by substantial morbidity and mortality, serves as a stark reminder of the pressing need for thorough understanding and effective management

of this condition. Although diabetes has long been acknowledged for its well-documented complications, notably neuropathy and retinopathy, recent research has revealed a compelling revelation in which a nuanced interplay exists between disrupted fatty acid metabolism and the intricacies of vascular microcirculatory impairments [2].

Fatty acids play critical roles in energy metabolism and serve as essential building blocks for various cellular components [3]. Under normal physiological conditions, fatty acid metabolism is tightly regulated, thereby ensuring a balanced supply of energy and lipid homeostasis [4]. However, in diabetes, this regulation falters, thus resulting in altered fatty acid profiles, abnormal lipid buildup, and heightened oxidative stress.

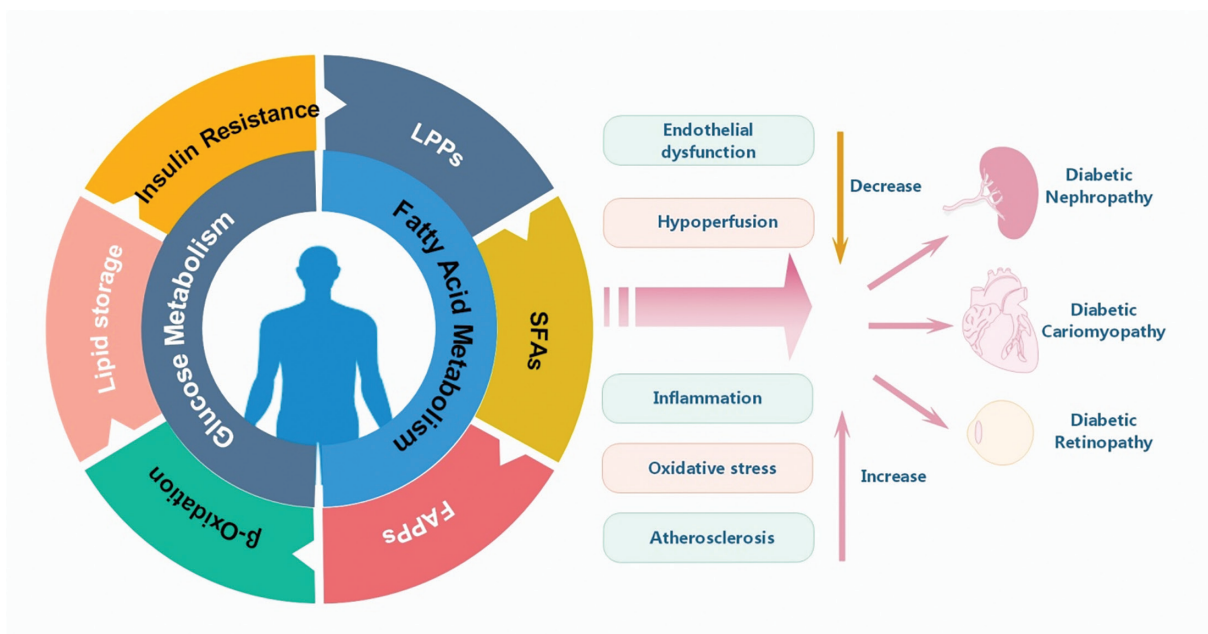
The microvasculature, consisting of small arterioles, capillaries, and veins, plays crucial roles in delivering oxygen and nutrients to tissues and facilitating waste removal [5, 6]. Understanding the intricate link between altered fatty acid metabolism and microcirculatory issues in diabetes is critical. Dysregulated fatty acid metabolism in diabetes disrupts microvascular function through various means, including increased production of harmful lipid byproducts, such as reactive oxygen species (ROS) and lipid peroxides. These disturbances

foster endothelial dysfunction and disrupt vascular equilibrium [7–9]. Moreover, changes in fatty acid composition and metabolism impair endothelial cells, thus decreasing nitric oxide availability and increasing inflammation [10].

This review is aimed at investigating the intricate link between altered fatty acid metabolism and microcirculatory impairments in diabetes, to ultimately enhance the quality of life of people living with diabetes (Figure 1).

## Mechanisms of Fatty Acid Metabolism Disorders in Diabetes Mellitus

Diabetes mellitus involves complex mechanisms leading to dysfunctional fatty acid metabolism, encompassing multiple interconnected factors [11, 12]. A critical element is the disruption of fatty acid oxidative metabolism. Impaired insulin signaling and decreased insulin sensitivity diminish cellular uptake and utilization of fatty acids, thus resulting in their accumulation in the bloodstream [13]. This dysregulation of fatty acid oxidation contributes to the elevated levels of saturated fatty acids, lipid peroxidation products,



**Figure 1** Overview of the Relationships Among Microvascular Dysfunction, Fatty Acid Metabolism, and Diabetes.

and fatty acid peroxidation products observed in people with diabetes [14].

Insulin resistance, another substantial contributor to impaired fatty acid metabolism in diabetes, decreases the responsiveness of target tissues to insulin's actions, including glucose uptake and lipid metabolism regulation. In insulin-resistant states, adipose tissue becomes resistant to insulin's inhibitory effect on lipolysis, and release of free fatty acids from adipocytes increases [15]. The excessive influx of fatty acids into non-adipose tissues, such as the liver and skeletal muscle, overwhelms the capacity for oxidation, and contributes to lipid accumulation and impaired metabolic homeostasis [16].

Alterations in adipogenesis are also involved in dysfunctional fatty acid metabolism in diabetes [17]. Dysfunctional adipose tissue, with enlarged adipocytes, inflammation, and altered adipokine secretion, disrupts lipid metabolism [18, 19]. Visceral adipocytes contribute to insulin resistance and metabolic disturbances. Increased lipolysis in visceral adipose tissue releases more fatty acids into circulation, and consequently exacerbates lipid accumulation in non-adipose tissues and impairs insulin action. Although less active, subcutaneous adipose tissue acts as a reservoir for excess fatty acids and aids in maintaining metabolic balance [20]. Insulin promotes lipogenesis, in which glucose is converted into fatty acids, and triglyceride hydrolysis increases; consequently, an imbalance between lipogenesis and lipolysis causes fatty acid buildup in the bloodstream and peripheral tissues.

## Microcirculation and Fatty Acid Metabolism Dysfunction in Diabetes

The microcirculation refers to the intricate network of small blood vessels, including microarteries and veins, where crucial exchanges occur between the bloodstream and tissues [21]. The microcirculation plays a critical role in matching blood flow to diverse tissue metabolic demands, thus ensuring proper perfusion and venous return regulation. Microcirculatory disturbances, such as altered blood properties, can lead to issues including vessel constriction, diminished blood flow, or clot formation. Consequently, local tissues may

have inadequate blood supply, which may result in ischemia, hypoxia, and even tissue necrosis.

Elevated levels of saturated fatty acids (SFAs), lipid peroxidation products (LPPs), and fatty acid peroxidation products (FAPPs) in diabetes directly harm microvascular function [22]. These metabolites affect endothelial cells, by causing oxidative stress, inflammation, and apoptosis [23]. They also hinder endothelial nitric oxide synthase activity; decrease nitric oxide levels; and lead to vasoconstriction, platelet aggregation, and leukocyte adhesion [24]. Moreover, they activate pro-inflammatory pathways, such as NF- $\kappa$ B, that produce cytokines and adhesion molecules, and consequently further damage the endothelium [25].

Fatty acid metabolism disorders affect pericytes, disrupting their function and survival through mitochondrial dysfunction and oxidative stress [26]. Pericyte loss leads to increased microvascular permeability, impaired blood flow regulation, and decreased capillary density, thereby contributing to microcirculatory disorders in diabetes [27–30].

Additionally, these metabolic disorders affect red blood cells (RBCs), by altering their membrane properties, deformability, and promoting aggregation. In diabetes, RBCs are exposed to elevated SFAs and oxidative stress [31, 32]. Oxidative stress caused by lipid peroxidation products can damage RBCs by causing hemolysis and release of free hemoglobin, thus further impairing vascular function and causing inflammation [33].

This bidirectional relationship between abnormal fatty acid metabolism and microcirculatory disorders in diabetes disrupts microvascular perfusion, oxygen delivery, and metabolic homeostasis; consequently leads to tissue hypoxia and activating hypoxia-inducible factors; and hinders fatty acid oxidation processes [34].

## Diabetic Fatty Acid Metabolism Disorders, Toxic End Products, and Microvascular Dysfunction

Disruptions in fatty acid metabolism in people with diabetes result in generation of a range of peroxidized lipids, predominantly LPPs and FAPPs. LPPs consist of malondialdehyde (MDA), formaldehyde, and pyruvic acid, whereas FAPPs encompass

4-hydroxy-2-nonenal (4-HNE), hydroperoxyoctadecadienoic acid (HPODE), malondialdehyde-acetaldehyde (MAA), and lipid peroxide (LPO), among others [35]. These metabolically toxic byproducts disturb cellular equilibrium, impair cellular structure and function, trigger inflammatory responses, and contribute to the initiation and progression of microcirculatory disorders.

High blood glucose and insulin levels in diabetes can lead to excess production and buildup of saturated fatty acids (SFAs), such as palmitic acid (PA), stearic acid (SA), and myristic acid. These SFAs induce oxidative stress and free radical generation in endothelial and vascular smooth muscle cells, thus worsening inflammation, cellular dysfunction, and damage [36]. Consequently, these effects can lead to abnormal microvascular dilation and increased permeability, which further compromise the normal functioning of the microvasculature.

### Lipid Peroxidation Products

LPPs, a diverse group of hydroxyl compounds generated during the hyperoxidation of lipids, are distinctive toxic metabolites associated with fatty acid metabolism disorders in diabetes mellitus [37]. The primary LPPs in people with diabetes are MDA, pyruvate, and formaldehyde. The presence of these LPPs elicits oxidative stress and triggers localized inflammatory responses, thereby accelerating cellular injury to vascular endothelial cells, smooth muscle cells, and platelets, and contributing to the development of microcirculatory disorders [38].

#### MDA

MDA levels have emerged as a valuable indicator for evaluating alterations in microcirculatory function and the progression of disorders, as demonstrated by studies emphasizing the strong correlation between MDA and microvascular dysfunction [39]. Vascular endothelial cells are directly impaired by MDA, thus leading to aberrant endothelial function and apoptosis. Additionally, MDA prompts macrophage infiltration into the microvasculature, and triggers the release of inflammatory factors, including interleukin-1 $\beta$  (IL-1 $\beta$ ) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [40]. These factors further contribute to the injury of endothelial cells and vascular smooth

muscle cells, and ultimately result in microvascular vasodilation. Importantly, the interaction between MDA and proteins or amino acids yields unstable carboxylation products known as advanced glycation end products, which induce oxidation and structural damage to cell membrane lipids, and negatively affect the normal functioning of the microvasculature [41]. Furthermore, studies have indicated that MDA promotes platelet aggregation, as well as the synthesis and release of thromboxane A<sub>2</sub>, and consequently stimulates platelet activation and thrombosis [42, 43]. Promising prospects include inhibiting malondialdehyde production and metabolism to enhance microvascular function and alleviate complications in people with diabetes.

#### Pyruvate

Pyruvic acid, an LPP derived from the breakdown of fatty acids and carbohydrates, is elevated in diabetes, and negatively affects vascular microcirculation. Pyruvic acid induces oxidative stress and inflammation in endothelial cells, thus leading to cell damage and diminished vascular dilation, and causing microcirculatory disturbances [44]. Additionally, PA inhibits the electron transport chain, thereby affecting energy metabolism and causing endothelial dysfunction and ischemia, and consequently vascular endothelial function [45]. Moreover, it influences platelet function, by increasing the risk of thrombus formation and potentially contributing to microcirculatory disorders [46].

#### Formaldehyde

Lipid peroxidation can lead to the oxidative degradation of fatty acids, phospholipids, and cholesterol, and the subsequent formation of a series of ROS and reactive metabolites including formaldehyde [39, 47]. Formaldehyde undergoes condensation reactions with biomolecules such as amino acids and nucleic acids and forms stable adducts, thus causing base and protein adducts, NA-interstrand crosslinks (ICLs), or DNA-protein crosslinks (DPCs) [48]. These adducts activate inflammatory responses, promote oxidative stress, and induce processes, such as cell apoptosis, and may lead to endothelial cell damage, vasoconstriction, and ultimately microcirculatory disorders. Additionally, formaldehyde

inhibits important metabolic enzymes such as pyruvate dehydrogenase and glutathione transferase, and consequently disrupts energy metabolism and redox balance. These may result in endothelial cell dysfunction and apoptosis, and further affect vascular function and microcirculation [49].

## FAPPs

Under hyperglycemia, excess glucose is oxidized in the mitochondria, which release large amounts of oxygen radicals that act on fatty acid molecules and eventually produce FAPPs. This class of very reactive oxidants causes microcirculatory disorders through a variety of mechanisms, including damage to membrane lipids, influence on cell signaling, and inhibition of enzyme activity. Typical FAPPs include 4-HNE, HPODE, MAA, and LPO [50, 51].

## 4-HNE

As a result of oxidative stress on fatty acids, the reactive metabolite 4-HNE is created. A major reason for 4-HNE generation is the diabetes condition [52]. Microvascular dysfunction can result from 4-HNE's effects on vascular endothelial cell function, including inhibition of nitric oxide generation and release from endothelial cells [53]. Second, 4-HNE directly affects smooth muscle cells, and may lead to vasoconstriction and exacerbation of the severity of microcirculatory disorders. In addition, 4-HNE triggers apoptosis and inflammatory reactions that increase the permeability of the vascular wall by producing and releasing a variety of inflammatory cytokines, thus causing tissue edema and microvascular leakage, as well as participating in the pathophysiological process of the emergence of microcirculatory disorders [54]. Inflammatory factors such as IL-6 and TNF- $\alpha$  further promote the generation of ROS and cytotoxic LPO products, which affect normal cellular function.

## HPODE

HPODE is a common FAPP and an important cause of microcirculatory disorder shown to cause platelet aggregation and lead to microvascular thrombosis [55]. In addition, HPODE harms the endothelium layer and hastens the development

of microcirculatory disorders by causing vascular endothelial cell apoptosis and increasing the inflammatory response [56]. Arachidonic acid, a polyunsaturated fatty acid, is a crucial part of the phospholipids that make up cell membranes. A variety of enzymes catalyze arachidonic acid oxidation into several bioactive compounds, including HPODE. In people with diabetes, HPODE increases the production of ROS clusters in macrophages and endothelial cells by activating NADPH oxidase and causing oxidative damage to endothelial cell mitochondria. Consequently, the oxidative stress response is enhanced, and vascular wall damage causes the development of microcirculatory disorders [57]. Therefore, the genesis and progression of microcirculatory disorders are significantly influenced by the abnormal production and accumulation of HOPDE in people with diabetes.

## MAA

The complex known as MAA, the complex formed through the interaction of byproducts from fatty acid peroxidation with aldehydes such as acetone or malondialdehyde, plays a pivotal role in the development of complications associated with diabetes [58]. MAA causes structural damage to the microvasculature in animal models of cardiovascular disease by inducing several inflammatory responses in endothelial, smooth muscle, and macrophage cells. Additionally, MAA prompts oxidative stress, inflammation, and responses and activation of the NF- $\kappa$ B signaling pathway; consequently, abnormal endothelial function and microvascular disorders may result [59]. Protection of the arteries is lost when MAA binds high-density lipoprotein, thus exacerbating endothelial cell damage and vascular disease [60].

## LPO

LPO is a class of oxidation products generated in fatty acid peroxidation reactions. Excess free fatty acids are absorbed into cells during the insulin-resistant stage of diabetes, in which fatty acid metabolism is disrupted, and peroxidation reactions increase. These reactions lead to the generation of LPO and other lipid peroxidation products [61]. LPO is believed to be a major cause of diabetic microcirculatory disorders. LPO has a variety of biological

effects, including altering the physicochemical characteristics of cell membranes, disturbing the integrity of membrane lipids, increasing the generation of free radicals, and accelerating the oxidative stress response [62]. Additionally, vasoconstriction and higher blood flow resistance can result from LPO's direct effects on the contractile activity of vascular smooth muscle cells [63]. The incidence of microvascular disorders in people with diabetes is highly correlated with LPO levels [64]. Therefore, decreasing LPO levels may enhance microcirculatory function in people with diabetes. LPO, a byproduct of oxidative stress and altered fatty acid metabolism in diabetes, plays a critical role in the emergence and advancement of microcirculatory disorders as well as the development of microvascular complications in people with diabetes.

### SFA

People with diabetes exhibit significantly elevated levels of SFA, which are associated with insulin resistance, malnutrition, and chronic inflammatory responses. Insulin resistance disrupts the storage of fatty acids within adipocytes, thus leading to their release into the blood. Malnutrition, a common concurrent symptom of diabetes, accelerates protein catabolism and causes abnormal fatty acid metabolism, thereby resulting in increased levels of certain substances in the body [65]. Chronic low-grade inflammation is frequently observed in people with diabetes and stimulates adipocytes to release fatty acids [66].

### Palmitic Acid

Several studies have found a significant elevation in PA levels in the serum in people with diabetes, a response closely associated with the occurrence of microvascular complications [67–69]. Additionally, PA induces endothelial dysfunction, increases leukocyte adhesion to endothelial cells, promotes inflammatory responses, and contributes to the development of microcirculatory disturbances. PA may also contribute to microcirculatory dysfunction by inducing oxidative stress. People with diabetes often experience oxidative stress, and excessive intake of PA may exacerbate oxidative stress and lead to microcirculatory dysfunction [70].

### SA

In people with a high-fat diet or diabetes, SA affects microcirculatory function by increasing oxidative stress and inflammatory responses in endothelial cells [71]. SA induces apoptosis of circulating vascular progenitor cells, which play a crucial role in microvascular formation [72]. Additionally, SA activates NLRP3 and consequently triggers inflammatory responses that impair endothelial cells and contribute to microcirculatory disturbances [73].

### Examination Methods

Microvascular complications associated with diabetes affect multiple organs throughout the body, including the kidneys, heart, brain, and eyes. The study of the correlation between cardiac and renal microvascular diseases relies on renal function tests, such as creatinine, glomerular filtration rate, and proteinuria, to quantify renal microvascular disease [74]. Positron emission tomography is considered the gold standard for non-invasive diagnostic imaging of cardiac microvascular disease. However, this method has several limitations, including high cost, radiation exposure, equipment requirements, restricted availability of isotopes, and relatively low spatial resolution [75]. Retinal lesions can be assessed with optical coherence tomography (OCT) to examine the condition of the retina [76]. OCT excels in imaging superficial structures, but has limited effectiveness in visualizing deep microvascular structures. Despite its high resolution capabilities, OCT may not capture the minute details of very small microvascular changes. Achieving optimal OCT imaging requires skilled operators with experience to ensure image quality and accuracy, thus rendering it operator-dependent. Conditions such as cataracts can diminish eye transparency, and consequently impair the quality of OCT imaging. Additionally, magnetocardiography (MCG) is a recent clinical examination method that can aid in the diagnosis of cardiac microvascular disorders [77]. MCG technology currently faces several limitations. First, it is not widely accessible in many healthcare institutions, because of its limited use. The high costs associated with acquiring and maintaining MCG equipment further hinder its use, particularly in resource-constrained regions. Similarly

to OCT, MCG has depth limitations that make it more suitable for evaluating superficial aspects of cardiac microvascular diseases but less effective for deeper structures. Although MCG holds promise, additional research is needed to validate its accuracy and clinical utility in diagnosing cardiac microvascular diseases. This method may not yet be a fully mature alternative to traditional diagnostic methods at this stage.

## Therapeutic Advances

The development of microcirculatory dysfunction in people with diabetes is closely associated with disturbances in fatty acid metabolism. Therefore, decreasing the production and effects of toxic metabolites derived from fatty acids is a crucial approach in preventing and treating diabetes-associated microcirculatory impairments. One strategy is to target the production and metabolism of LPPs and FAPPs, such as by using antioxidants, scavenging free radicals, and decreasing the formation of lipid peroxidation products. For example, ginsenoside protects against renal failure in diabetes through decreasing oxidative stress biomarkers (GPX, MDA, and SOD) [40]. Selenium and resveratrol reverse the decreases in GSH and GSH-Px levels, the decline in optic nerve activity, the decrease in vitamin A levels, and the occurrence of lipid peroxidation and apoptosis induced by STZ [78]. Another strategy is controlling the levels of SFA, for example, through modification of the dietary composition, physical exercise, or medication. Nevertheless, most of these therapeutic approaches remain in preclinical research stages and require further clinical validation to establish their efficacy. However, they provide promising novel avenues for the prevention and management of microcirculatory impairments induced by diabetes.

## Summary

The intricate relationship between disrupted fatty acid metabolism and microcirculatory disorders in diabetes highlights the need for further research to advance understanding of the underlying mechanisms and to develop more effective therapeutic approaches. Targeting the production and

metabolism of lipid peroxidation products and fatty acid peroxidation products through interventions such as antioxidant therapy and inhibition of lipid peroxidation product formation holds promise as a potential therapeutic strategy. Regulating the levels of saturated fatty acids through dietary modifications, exercise regimens, or pharmacological interventions may also be a viable approach. Moreover, recent advancements in identifying therapeutic agents offer hope for improved treatment outcomes. Comprehensive investigations of the effects of disrupted fatty acid metabolism on the microvasculature in diabetes will be critical to pave the way to the development of novel therapeutic strategies that enhance the quality of life and prognosis of patients with diabetes. These endeavors are expected to contribute to addressing the major challenges in managing fatty acid metabolism disorders in diabetes mellitus and their critical implications on microcirculatory health.

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## Conflict of Interest

No conflicts of interest to declare.

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