Association between Microvascular dysfunction, Fatty Acid Metabolism, and Diabetes

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Conflicts of Interest

No conflict of interest to declare

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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. It represents a major global health concern due to its increasing prevalence and significant morbidity and mortality. This review explores the relationship 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 aims to contribute to future research and the development of effective strategies for preventing and managing diabetes-related microcirculatory impairments, ultimately

enhancing the quality of life for individuals living with diabetes.

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

Introduction

Nowadays, the worldwide prevalence of diabetes in adults is approximately 382 million, and it is anticipated to surge to 592 million by the year 2035[1]. Its escalating prevalence, coupled with substantial morbidity and mortality, underscores the urgent need for comprehensive understanding and management.The age group most significantly affected by diabetes comprises individuals aged between 40 and 59 years. Moreover, over 80% of individuals with diabetes are located in low- and middle-income countries[1]. While diabetes is widely recognized for its established complications, including neuropathy, and retinopathy, recent research has shed light on the intricate interplay between altered fatty acid metabolism and vascular microcirculatory impairments[2]. Exploring this association is of paramount importance, as it contributes to a more comprehensive understanding of the vascular consequences of diabetes and offers potential avenues for targeted interventions.

Fatty acids play a critical role in energy metabolism and serve as essential building blocks for various cellular components[3]. Under normal physiological conditions, fatty acid metabolism is tightly regulated, ensuring a balanced supply of energy and lipid homeostasis[4]. However, in the context of diabetes, there is an impairment in the regulation of fatty acid metabolism, leading to changes in fatty acid profiles, abnormal lipid accumulation, and increased oxidative stress.

Microvascular, consisting of small arterioles, capillaries, and veins, plays a crucial role in delivering oxygen and nutrients to tissues and facilitating waste removal[5, 6]. Understanding the intricate relationship between altered fatty acid metabolism and microcirculatory impairments in diabetes is of paramount importance. The dysregulation of fatty acid metabolism in diabetes leads to microvascular dysfunction through various mechanisms, including increased production of lipid peroxidation

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products, such as reactive oxygen species (ROS) and lipid peroxides, promoting endothelial dysfunction and disrupting vascular homeostasis[7-9]. Additionally, changes in fatty acid composition and metabolism impair endothelial cell function, leading to decreased availability of nitric oxide and increased inflammation[10].

In this review, our objective is to explore the current understanding of the relationship between altered fatty acid metabolism and microcirculatory impairments in diabetes. We will investigate the underlying mechanisms, assess the impact on microvascular function, and explore potential therapeutic interventions that could mitigate these complications. By gaining insights into this intricate interplay, we aim to contribute to future research and the development of effective strategies for preventing and managing diabetes-related microcirculatory impairments, ultimately enhancing the quality of life for individuals living with diabetes.

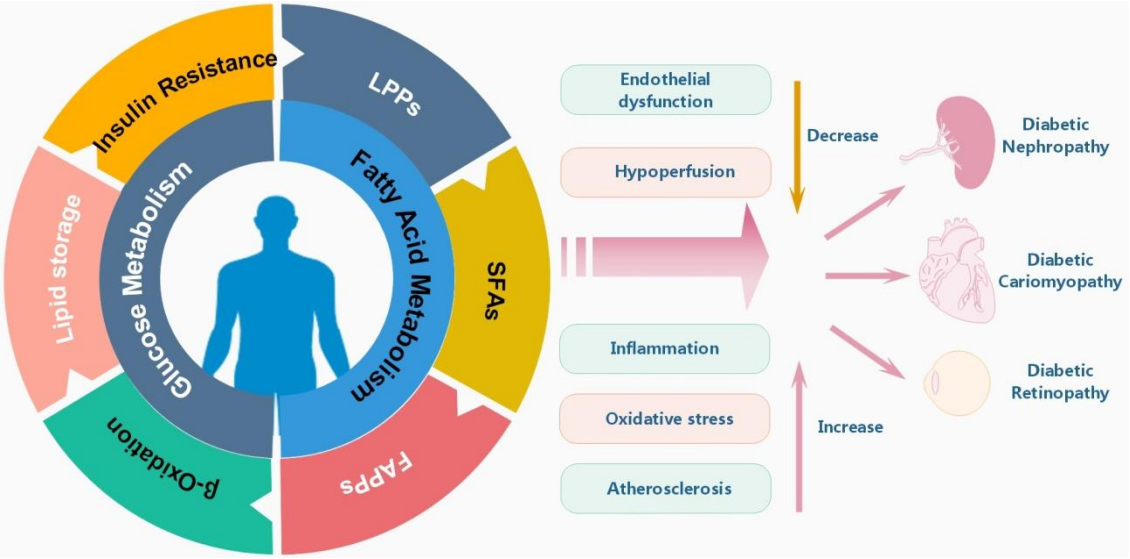

Figure 1. An Over-view of the relationship between Microvascular dysfunction, Fatty Acid Metabolism, and Diabetes

1. Mechanisms of Fatty Acid Metabolism Disorders in Diabetes Mellitus

In diabetes mellitus, the mechanisms underlying fatty acid metabolism dysfunction are multifaceted and involve various interrelated factors[11, 12]. One crucial aspect is the disruption in fatty acid oxidative metabolism. Impaired insulin signaling and decreased insulin sensitivity lead to reduced uptake and utilization of fatty acids by the cells, resulting in their accumulation in the blood[13]. This dysregulation in fatty

acid oxidation contributes to the elevated levels of saturated fatty acids, lipid peroxidation products, and fatty acid peroxidation products observed in individuals with diabetes[14].

Another significant contributor to fatty acid metabolism dysfunction in diabetes is insulin resistance, which will decrease responsiveness of target tissues to the actions of insulin, including its effects on promoting glucose uptake and regulating lipid metabolism. In insulin-resistant states, adipose tissue becomes resistant to the inhibitory effect of insulin on lipolysis, leading to increasing release of free fatty acids from adipocytes[15]. Consequently, the excessive influx of fatty acids into non-adipose tissues, such as the liver and skeletal muscle, overwhelms their capacity for oxidation, contributing to lipid accumulation and impaired metabolic homeostasis[16].

Adipogenesis changes contribute to dysfunctional fatty acid metabolism in diabetes[17]. Dysfunctional adipose tissue, with enlarged adipocytes, inflammation, and altered adipokine secretion, disrupts lipid metabolism[18]. Visceral adipocytes play a role in promoting insulin resistance and metabolic disturbances. Increased lipolysis in visceral adipose tissue releases more fatty acids into circulation, exacerbating lipid accumulation in non-adipose tissues and impairing insulin action. Subcutaneous adipose tissue, while less active, acts as a reservoir for excess fatty acids, helping maintain metabolic balance [19]. Insulin promotes lipogenesis, converting glucose into fatty acids, and increasing triglyceride hydrolysis, leading to an imbalance between lipogenesis and lipolysis, causing fatty acid buildup in the bloodstream and peripheral tissues.

2. Microcirculation and Fatty Acid Metabolism Dysfunction in Diabetes

The microcirculation refers to the intricate network of small blood vessels, including micro arteries and veins, where vital exchanges occur between the bloodstream and tissues[20]. It plays a crucial role in facilitating the exchange of substances, such as oxygen, nutrients, and waste products, between the blood and the surrounding tissues. Functionally, the microcirculation ensures that blood flow is appropriately matched to the metabolic demands of different tissues and organs, maintaining adequate perfusion and regulating the return of blood to the heart. However, when the microcirculation

encounters disturbances, such as alterations in the physical and chemical properties of blood, it can lead to various complications. These disruptions may manifest as constriction of vessel lumens, reduced blood flow velocity, or the formation of blood clots. As a consequence, local tissues may suffer from inadequate blood supply, resulting in ischemia, hypoxia, and even tissue necrosis.

Elevated levels of saturated fatty acids (SFAs), lipid peroxidation products (LPPs), and fatty acid peroxidation products (FAPPs) observed in diabetes directly affect various cellular components within the microvascular, leading to impaired microvascular function[21]. The link between fatty acid metabolism and microvascular dysfunction in diabetes involves complex mechanisms that contribute to the development and progression of vascular complications[22].

One important aspect is the impact of these aberrant metabolites on endothelial cells, which line the inner surface of blood vessels. SFAs, LPPs, and FAPPs can induce endothelial dysfunction by promoting oxidative stress, inflammation, and apoptosis[23]. They impair endothelial nitric oxide synthase (eNOS) activity, reducing nitric oxide (NO) bioavailability, and promoting vasoconstriction, platelet aggregation, and leukocyte adhesion[24].Additionally, these metabolites activate various pro-inflammatory signaling pathways, such as nuclear factor kappa B (NF-κB), leading to the production of inflammatory cytokines and adhesion molecules that further contribute to endothelial dysfunction and microvascular damage [25].

Disorders of fatty acid metabolism also affect the integrity and function of pericytes[26]. In diabetes, elevated levels of SFAs, LPPs, and FAPPs disrupt pericyte function and survival[27] through mechanisms involving mitochondrial dysfunction, oxidative stress, and activation of apoptotic pathways [28, 29]. Pericyte loss leads to increased microvascular permeability, impaired blood flow regulation, and reduced capillary density, contributing to microcirculatory disorders observed in diabetes[30].

Furthermore, disorders of fatty acid metabolism impact the function of red blood cells (RBCs), which are essential for oxygen delivery to tissues. In diabetes, RBCs are exposed to elevated levels of SFAs and oxidative stress[31, 32]. SFAs can alter RBC membrane fluidity, impair deformability, and promote RBC aggregation, leading to

reduced microvascular blood flow and tissue hypoxia. Additionally, oxidative stress induced by lipid peroxidation products can damage RBCs, causing hemolysis and the release of free hemoglobin, which further contributes to vascular dysfunction and inflammation[33].

The relationship between abnormal fatty acid metabolism and microcirculatory disorders in diabetes is bidirectional and interdependent. Impaired microvascular perfusion and inadequate oxygen delivery result in tissue hypoxia and disruptions in metabolic homeostasis. These hypoxic conditions activate hypoxia-inducible factors, which in turn promote lipid accumulation and hinder fatty acid oxidation processes[34].

3. Diabetic Fatty Acid Metabolism Disorders, Toxic End Products, and Microvascular dysfunction

Disruptions in fatty acid metabolism in individuals with diabetes give rise to the generation of a range of peroxidized lipids, predominantly including LPPs and FAPPs. LPPs consist of malondialdehyde (MDA), formaldehyde, and pyruvic acid, while FAPPs encompass 4-hydroxy-2-nonenal (4-HNE), hydroperoxyoctadecadienoic acid (HPODE), malondialdehyde-acetaldehyde (MAA), lipid peroxide (LPO), among others[35]. These metabolically toxic byproducts possess the capability to disturb cellular equilibrium, impair cellular structure and function, trigger inflammatory responses, and contribute to the initiation and progression of microcirculatory disorders.

Furthermore, elevated levels of blood glucose and insulin in diabetes patients can result in excessive production and accumulation of SFAs such as palmitic acid (PA), stearic acid (SA), and myristic acid (MA). These SFAs have the potential to induce oxidative stress and generate free radicals within endothelial cells and vascular smooth muscle cells, thereby exacerbating the inflammatory response in endothelial cells and leading to cellular dysfunction and damage [36]. Consequently, these effects can lead to abnormal microvascular dilation and increased permeability, further compromising the normal functioning of the microvascular.

3.1 Lipid peroxidation products

LPPs, a diverse group of hydroxyl compounds generated during the hyperoxidation of

lipids, represent the distinctive toxic metabolites associated with fatty acid metabolism disorders in diabetes mellitus[37]. These LPPs possess high reactivity, an affinity for binding to cell membranes and proteins, and the capacity to modulate the intracellular milieu and impact cellular functionality. Among the primary LPPs found in diabetic patients 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, thereby contributing to the development of microcirculatory disorders[38].

3.1.1 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]. Promising prospects lie in inhibiting malondialdehyde production and metabolism to enhance microvascular function and alleviate complications in individuals with diabetes. Vascular endothelial cells are directly impaired by MDA, leading to aberrant endothelial function and apoptosis. Additionally, MDA prompts macrophage infiltration into the microvasculature, thereby triggering the release of inflammatory factors, including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α)[40]. These factors further contribute to the injury of endothelial cells and vascular smooth muscle cells, ultimately resulting in microvascular vasodilation. Importantly, the interaction between MDA and proteins or amino acids yields unstable carboxylation products known as advanced glycation end products (AGEs). AGEs induce oxidation and structural damage to cell membrane lipids, thereby increasing membrane permeability and exacerbating cellular dysfunction. This compromised membrane permeability negatively affects the normal functioning of the microvasculature [41]. Furthermore, MDA exhibits potential for inducing thrombosis and activating platelets[42]. Studies have uncovered that MDA promotes platelet aggregation, as well as the synthesis and release of thromboxane A2, thereby stimulating platelet activation and thrombosis [43].

3.1.2 Pyruvate

Pyruvic acid, an LPP derived from the breakdown of fatty acids and carbohydrates, shows elevated levels in diabetes, negatively impacting vascular microcirculation. It can induce oxidative stress and inflammation in endothelial cells, leading to cell damage and reduced vascular dilation, causing microcirculatory disturbances[44]. Additionally, PA can inhibit the electron transport chain, affecting energy metabolism and causing endothelial dysfunction and ischemia, further impacting vascular endothelial function [45]. Moreover, it can influence platelet function, increasing the risk of thrombus formation and potentially contributing to microcirculatory disorders[46].

3.1.3 Formaldehyde

Lipid peroxidation can lead to the oxidative degradation of fatty acids, phospholipids, and cholesterol, resulting in the formation of a series of reactive oxygen species and reactive metabolites, including formaldehyde[39, 47]. Formaldehyde can undergo condensation reactions with biomolecules such as amino acids and nucleic acids, forming stable adducts, thereby causing dysfunction in proteins and nucleic acids[48]. These adducts may activate inflammatory responses, promote oxidative stress, and induce processes like cell apoptosis, leading to endothelial cell damage, vasoconstriction, and ultimately microcirculatory disorders. Additionally, formaldehyde can inhibit important metabolic enzymes such as pyruvate dehydrogenase and glutathione transferase, disrupting energy metabolism and redox balance. These changes can result in endothelial cell dysfunction, apoptosis, and further impact vascular function and microcirculation[49].

3.2 FAPPs

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

3.2.1 4-HNE

As a result of oxidative stress on fatty acids, the reactive metabolite 4-HNE is created. According to studies, one of the main reasons for 4-HNE generation is the diabetes condition[52]. Microvascular dysfunction can result from 4-HNE's impact on vascular endothelial cell function, which inhibits NO generation and release from endothelial cells[53]. Second, 4-HNE can directly impact smooth muscle cells, which might lead to vasoconstriction and exacerbate the severity of microcirculatory disorders. In addition, 4-HNE can trigger apoptosis and inflammatory reactions that increase the permeability of the vascular wall by producing and releasing a variety of inflammatory cytokines, 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-α can further promote the generation of reactive oxygen species (ROS) and cytotoxic lipid peroxidation (LPO) products, affecting normal cellular function.

3.2.2 HPODE

HPODE is a common FAPP and an important cause of microcirculatory disorder, which has been shown to cause platelet aggregation, leading to in microvascular thrombosis[55]. Also, HPODE can harm the endothelium layer and hasten the development of microcirculatory disorders by causing vascular endothelial cells to apoptosis and an increase in the inflammatory response[56]. Arachidonic acid (AA), a polyunsaturated fatty acid, is a crucial part of the phospholipids that make up cell membranes. A variety of enzymes can catalyze AA's oxidation into a number of bioactive compounds, including HPODE. In diabetic patients. Studies have shown that HPODE can increase the production of ROS clusters in macrophages and endothelial cells by activating NADPH oxidase (NOX) and causing oxidative damage to endothelial cell mitochondria. This results in an enhanced oxidative stress response and damages the vascular wall, which 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 diabetic patients.

3.2.3 MAA

The complex known as MAA, which is generated when the byproducts of fatty acid peroxidation products with aldehydes such as acetone or malondialdehyde, plays an important role in the development of complications related to diabetes[58]. It has been found that MAA causes structural damage to the microvascular in animal models of cardiovascular disease by inducing a number of inflammatory responses in endothelial, smooth muscle, and macrophage cells. Additionally, MAA prompts oxidative stress, inflammation, responses and activation of the NF-κB signaling pathway, leading to abnormal endothelial function and microvascular disorders[59]. High-density lipoprotein (HDL) protection for the arteries is lost when MAA binds to HDL, exacerbating endothelial cell damage and vascular disease[60].

3.2.4 LPO

LPO is a class of oxidation products generated in fatty acid peroxidation reactions. Excess free fatty acids are absorbed into the cells during the insulin-resistant stage of diabetes, which disrupts fatty acid metabolism and increases peroxidation reactions. These reactions lead to the generation of LPO and other lipid peroxidation products[61]. One of the main causes of diabetic microcirculatory disorders is thought to be LPO. 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, among others[62]. Additionally, vasoconstriction and higher blood flow resistance can result from LPO's direct impact on the contractile activity of vascular smooth muscle cells[63]. Incidence of microvascular disorders in diabetic individuals is highly correlated with LPO levels[64]. Therefore, reducing LPO levels may help in enhancing diabetic patients' microcirculatory function. 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 diabetic patients.

3.3 SFA

Patients 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, leading to their release into the blood. Malnutrition is a common concurrent symptom of diabetes, accelerating protein catabolism and causing abnormal fatty acid metabolism, resulting in increased levels [65]. Chronic low-grade inflammation is frequently observed in diabetic patients and stimulates adipocytes to release fatty acids [66].

3.3.1 Palmitic acid

Several studies have found a significant elevation of palmitic acid (PA) levels in the serum of diabetic patients, which is closely related to the occurrence of microvascular complications [67-69]. Additionally, research has shown that PA can induce endothelial dysfunction, increase leukocyte adhesion to endothelial cells, and promote inflammatory responses, thus contributing to the development of microcirculatory disturbances. PA may also contribute to microcirculatory dysfunction by inducing oxidative stress. Diabetic patients often experience oxidative stress, and excessive intake of PA may exacerbate oxidative stress, leading to microcirculatory dysfunction [70].

3.3.2 SA

In cases of high-fat diet or diabetes, SA can impact microcirculatory function by increasing oxidative stress and inflammatory responses in endothelial cells[71]. Studies have revealed that SA induces apoptosis of circulating vascular progenitor cells, which play a crucial role in microvascular formation [72]. Additionally, SA can activate the NLRP3, triggering inflammatory responses that impair endothelial cells and contribute to microcirculatory disturbances [73].

4. Examination Methods

Microvascular complications associated with diabetes can 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 examines such as creatinine, glomerular filtration rate, and proteinuria to quantify renal microvascular disease[74]. PET (positron emission tomography) is considered the gold standard for non-invasive diagnostic imaging of cardiac microvascular disease (CMVD). However, it also presents certain limitations, including high cost, radiation

exposure, equipment requirements, restricted availability of isotopes, and relatively lower spatial resolution[75]. Retinal lesions can be assessed using optical coherence tomography (OCT) to examine the condition of the retina. Additionally, Magnetocardiography (MCG) is a recent clinical examination method that can aid in the diagnosis of cardiac microvascular disorders[76].

5.Therapeutic Advances

The development of microcirculatory dysfunction in diabetic patients is closely linked to disturbances in fatty acid metabolism. Therefore, reducing the production and effects of toxic metabolites derived from fatty acids represents 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 using antioxidants, scavenging free radicals, and reducing the formation of lipid peroxidation products. Another strategy is to control the levels of SFA, for example, by modifying dietary composition, engaging in physical exercise, or using medication. Additionally, there have been emerging potential effective therapeutic drugs in recent years[40, 77-79]. Nevertheless, it should be noted that most of these therapeutic approaches are still in the preclinical research stage 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.

6. Summary

The intricate relationship between disrupted fatty acid metabolism and microcirculatory disorders in diabetes highlights the need for further research to advance our 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 also represents a viable approach. Moreover, recent advancements in

identifying therapeutic agents offer hope for improved treatment outcomes. It is essential to undertake comprehensive investigations into the impact of disrupted fatty acid metabolism on microvascular in diabetes to pave the way for the development of novel therapeutic strategies that can enhance the quality of life and prognosis of individuals with diabetes. These endeavors will contribute to addressing the forefront challenges and importance of managing fatty acid metabolism disorders in diabetes mellitus and their implications on microcirculatory health.

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