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The Vicious Cycle Between Lipid Metabolism Disorder and Podocyte Injury in Diabetic Nephropathy

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Abstract: ***Diabetes mellitus (DM) is a common chronic metabolic disease, and diabetic kidney disease (DKD) is one of its major complications. At present, an estimated 589 million people worldwide suffer from diabetes. It is predicted that the number of diabetic patients will rise to 853 million by 2050, among whom 30% to 40% will develop DKD and eventually progress to end-stage renal disease (ESRD). In China, the number of adult diabetic patients aged 20 to 79 reaches 148 million, ranking first globally. DKD has become the second leading cause of ESRD after glomerulonephritis, accounting for 19% of all ESRD cases. Studies have confirmed that dyslipidemia participates in the occurrence and progression of DKD and is closely correlated with DKD. Dysregulated lipid metabolism often leads to dysfunction of specific target organs such as the heart and kidneys. Podocytes are highly differentiated cells attached to the outer side of the glomerular basement membrane (GBM) and are the most vulnerable cells in the glomerulus. Podocytes are sensitive to abnormal lipid accumulation. Excessive intracellular lipid accumulation will trigger podocyte dysfunction, cytoskeleton rearrangement, inflammatory responses and ultimately podocyte death. This paper reviews the mechanisms and interactions of DKD, lipid metabolism disorder and podocyte injury reported in recent years, so as to provide new ideas for the treatment of DKD.***

Keywords: Lipid Metabolism Disorder, Podocyte Injury, Diabetic Nephropathy.

1. Lipid Metabolism Disorder Induces Podocyte Injury

1.1 Direct Toxicity Caused by Lipid Accumulation

Modern pathology holds that renal lipid accumulation is an important factor leading to renal injury in diabetic nephropathy (DN). High levels of lipids in the human body can cause renal adipose deposition, glomerulosclerosis, endothelial activation and mesangial expansion, accelerate the progression of proteinuria and tubulointerstitial fibrosis, and directly damage podocytes, resulting in irreversible impairment of renal function [1].

1.1.1 Imbalanced Cholesterol Metabolism

Dyslipidemia is an important factor in the progression of DN, characterized by quantitative and qualitative changes in lipids and lipoproteins. Insulin resistance prompts adipose tissue to release a large amount of free fatty acids (FFA). FFAs promote the liver to synthesize more very low-density lipoprotein (VLDL), which relatively increases the content of cholesterol-rich low-density lipoprotein (LDL). Meanwhile, lipoprotein lipase (LPL) prolongs the clearance time of total triglycerides (TG). These changes jointly raise the levels of TG and VLDL. Glycation of high-density lipoprotein (HDL), as well as the inverse correlation between VLDL and HDL in TG exchange, further reduces HDL levels. Therefore, the main manifestations of dyslipidemia in DN patients are elevated TG, normal or elevated total cholesterol (TC), decreased HDL and increased LDL [2]. By establishing an early DKD rat model induced by high-fat and high-sugar diet combined with STZ, Hou et al. [3] revealed that abnormal accumulation of intracellular cholesterol ester (CE) in podocytes is a key pathological feature: CE deposition reduces cell membrane fluidity, hinders the dynamic remodeling of foot processes, induces massive mitochondrial ROS production, degrades key slit diaphragm proteins, impairs the filtration barrier function of podocytes and aggravates proteinuria. In addition, CE accelerates podocyte apoptosis by releasing factors such as IL-1β through the TLR4/NF-κB pathway. A study involving 15,000 patients with type 2 diabetes conducted by Russo et al. [4] showed that the risks of low glomerular filtration rate (GFR) and proteinuria rise linearly with the increase of TG levels or the decrease of HDL-C levels. Dyslipidemia related to diabetes-induced atherosclerosis (AS) promotes the occurrence and progression of DKD. However, some scholars believe that this may be related to gender, genetic factors and other factors, which needs further exploration.

1.1.2 Abnormal Metabolism of Triglycerides and Fatty Acids

Approximately 50% of patients with chronic kidney disease (CKD) have hypertriglyceridemia, and free fatty acids (FFA) and glycerol are the main components of triglycerides (TG) [5]. FFAs stored in lipid droplets in the form of triglycerides can effectively protect cells from damage. On the contrary, excessive accumulation of FFAs plays a key role in podocyte injury and proteinuria formation [6]. Under high glucose and insulin-resistant conditions, the expression and activity of sterol regulatory element-binding protein 1c (SREBP-1c) are significantly upregulated, which further promotes the expression of fatty acid synthase (FAS) and acetyl-CoA carboxylase, accelerates TG synthesis and leads to abnormal lipid accumulation in podocytes [7]. At the same time, the activity of peroxisome proliferator-activated receptor α (PPARα) is inhibited, resulting in decreased expression of its downstream target gene carnitine palmitoyl transferase 1A (CPT1A). The β-oxidation of fatty acids in mitochondria is blocked, leading to abnormal accumulation of lipid droplets in podocytes, promoting podocyte apoptosis and shedding, and

aggravating the progression of diabetic nephropathy [8]. Under insulin resistance induced by high-fat diet, Cornejo et al. [9] found significant accumulation of TG and FFA in the glomeruli of OLETF rats, accompanied by destruction of podocyte structures such as foot process fusion, decreased expression of nephrin and podocin, and elevated urinary albumin. Calorie restriction reduced TG levels and restored lipolysis, but partial podocyte injury remained, suggesting that TG/FFA accumulation is a key driving factor for early podocyte injury. Kampe et al. [10] found that inhibition of CPT1A and downstream targets of AMP-activated protein kinase (AMPK) increases the mortality of podocytes induced by palmitic acid.

1.1.3 Other Lipid Metabolic Disorders

As a core intermediate product of sphingolipid metabolism, ceramide synthesis pathway can be significantly activated under high glucose and insulin-resistant conditions, leading to abnormal elevation of ceramide levels in podocytes. On the one hand, ceramide can be directly inserted into the podocyte membrane, destroy the fluidity and integrity of the membrane, and damage the structure of slit diaphragm proteins; on the other hand, as a signaling molecule, it can activate downstream apoptotic pathways, upregulate the Bax/Bcl-2 ratio and activate caspase-3 to induce programmed death of podocytes. Relevant studies [11] have shown that in patients with obesity-related glomerulopathy, ceramide accumulates in podocytes to produce reactive oxygen species (ROX), and ultimately induces mitochondrial damage.

1.2 Oxidative Stress Aggravates Lipid Peroxidation

Under persistent high glucose conditions, a large amount of ROS is produced, enhancing lipid peroxidation and generating highly reactive aldehydes such as 4-hydroxynonenal (4-HNE). These active aldehydes covalently modify key cytoskeletal proteins of podocytes such as nephrin and podocin, alter their structures and functions, destroy the integrity of slit diaphragms, directly impair the glomerular filtration barrier and cause proteinuria. Nicotinamide adenine dinucleotide phosphate oxidases (NOX) are transmembrane proteins that transfer electrons on biological membranes to generate superoxide anions, which are the main source of cellular ROS. Overexpression of NOX1, NOX4 and NOX5 can cause podocyte injury and promote the occurrence and progression of DN. High glucose stimulates the body to produce advanced glycation end products (AGEs), which bind to AGE receptors and activate NOX to generate massive ROS. In addition, the body can also activate NOX through the polyol pathway and protein kinase C (PKC) pathway, resulting in excessive ROS production. Studies have shown [12] that high glucose and TGF-β1 induce NOX4 expression, thereby causing the production and accumulation of ROS.

1.3 Organelle Dysfunction

The kidney is one of the organs with the highest mitochondrial content and oxygen consumption. In DKD experimental models, mitochondrial ATP content decreases and synthesis slows down. As a highly energy-dependent cell type, insufficient ATP directly affects the dynamic balance of podocyte cytoskeleton and the integrity of slit diaphragms, and eventually leads to podocyte shedding from the basement membrane. Excessive lipid accumulation disrupts the function of the electron transport chain (ETC), significantly reducing the efficiency of oxidative phosphorylation and leading to insufficient ATP synthesis. The decline of mitochondrial fatty acid oxidation and oxidative phosphorylation activity results in reduced energy output and mitochondrial biogenesis. Qin et al. [13] performed dual immunofluorescence analysis of mitochondrial voltage-dependent anion channels and nephrin on renal tissue sections of DN patients and control groups. The results indicated that the number of podocytes and mitochondrial content in glomeruli of DN patients were significantly reduced, and similar results were obtained in db/db mouse samples. Hyperglycemia is the most direct and major risk factor for the occurrence and progression of DN. Insulin resistance induced by hyperglycemia leads to abnormal glucose metabolism and activates alternative glucose metabolic pathways such as the polyol pathway and hexosamine pathway, further resulting in the accumulation of toxic intermediate products such as sorbitol and diacylglycerol [14]. Excessive sorbitol is oxidized to fructose under the action of sorbitol dehydrogenase, ultimately generating a large amount of ROS. Furthermore, fructose promotes the production of AGEs. Massive AGEs bind to their receptors and activate intracellular signaling pathways such as phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) and NF-κB, inducing oxidative stress and inflammatory cascade reactions. These pathological processes lead to structural damage and dysfunction of most renal cells. In terms of endoplasmic reticulum, lipid overload triggers endoplasmic reticulum stress and activates the unfolded protein response (UPR). Activated inositol-requiring enzyme 1α (IRE1α) can specifically splice an intron of 26 bases from X-box binding protein 1 (XBP1) mRNA, changing the open reading frame of XBP-1 mRNA. Its translation product XBP-1 can promote the expression of UPR target molecules containing endoplasmic reticulum stress response elements such as GRP78 to alleviate or terminate endoplasmic reticulum stress and restore intracellular homeostasis [15]. When stress persists, the expression of C/EBP homologous protein (CHOP) will be induced. As a transcription factor regulating cell apoptosis, CHOP can lead to programmed death of podocytes. Relevant studies have confirmed [16] that inhibiting the overactivation of the PERK/ATF4/CHOP pathway in podocytes can alleviate endoplasmic reticulum stress, thereby suppressing podocyte apoptosis and exerting a protective effect on podocytes. 1.4 Exosome-Mediated Interorgan Communication Under insulin-resistant conditions, the content of miR-27a in exosomes secreted by adipocytes increases significantly. These exosomes reach the kidney through the circulatory system and are then taken up by podocytes. miR-27a specifically binds to the 3' untranslated region of PPARγ mRNA to inhibit PPARγ expression, thereby weakening fatty acid oxidation capacity and aggravating intracellular lipid accumulation in podocytes [17]. In high glucose-induced mouse models, knockout or inhibition of miR-27a can restore PPARγ expression, improve fatty acid oxidation, and significantly reduce lipid accumulation and apoptosis in podocytes [18]. Meanwhile, when podocytes are injured by lipotoxicity, they release damage-associated molecular patterns (DAMPs) such as high mobility group box 1 (HMGB1). HMGB1 binds to toll-like

receptor 4 (TLR4) and advanced glycation end product receptor (RAGE) on the surface of macrophages, activates the NF-κB signaling pathway, and promotes macrophages to polarize into pro-inflammatory M1 type. These activated M1 macrophages secrete a large number of pro-inflammatory factors such as TNF-α and IL-6, which further aggravate podocyte injury and glomerular inflammatory response, forming a positive feedback loop.

2. Podocyte Injury Aggravates Lipid Metabolism Disorder

2.1 Effects of Inflammatory Factors on Lipid Metabolism

Pathologically injured podocytes continuously release pro-inflammatory factors such as TNF-α and IL-6 into the circulatory system. These inflammatory mediators activate hormone-sensitive lipase (HSL) in adipocytes to promote triglyceride hydrolysis, resulting in a significant increase in plasma free fatty acids (FFAs). Elevated FFAs, on the one hand, activate inflammatory signaling pathways such as PKC and NF-κB, inhibit tyrosine phosphorylation of insulin receptor substrate (IRS) and induce hepatic insulin resistance; on the other hand, FFAs promote excessive synthesis and secretion of very low-density lipoprotein (VLDL), forming a vicious cycle of lipid metabolism.

2.2 Exosome-Mediated Systemic Metabolic Regulation

Exosomes rich in microRNA (miRNA) released by injured podocytes enter the circulatory system and induce lipid metabolism disorder through two key pathways. On the one hand, after these exosomes are taken up by hepatocytes, specific miRNAs they carry (such as miR-30c and miR-148a) target and inhibit the expression of low-density lipoprotein receptor (LDLR), significantly reducing the liver's ability to clear circulating LDL and leading to hypercholesterolemia. At the same time, some miRNAs may reduce bile acid synthesis by inhibiting cholesterol 7α-hydroxylase (CYP7A1), further aggravating abnormal cholesterol metabolism. On the other hand, podocyte-derived exosomal miR-27a is taken up by adipocytes, inhibits the PPARγ signaling pathway, not only hinders the differentiation and maturation of adipocytes, but also upregulates the expression of adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), thereby promoting lipolysis and increasing the release of free fatty acids (FFAs). These FFAs enter the circulation and easily aggravate hepatic lipid deposition and insulin resistance [19].

2.3 Overactivation of Renin-Angiotensin-Aldosterone System (RAAS)

The renin-angiotensin-aldosterone system (RAAS) is the classic hemodynamic pathway, and its core effector molecule angiotensin II (Ang II) is also recognized as a key pathological factor causing podocyte injury. Podocyte injury leads to excessive activation of local RAAS and a significant increase in Ang II levels. Ang II interferes with lipid metabolism through multiple pathways: on the one hand, it directly inhibits the activity of adipose triglyceride lipase (ATGL) in adipose tissue, thereby reducing lipolysis; on the other hand, it stimulates hepatic synthesis and secretion of VLDL, and promotes adrenal aldosterone secretion to further aggravate insulin resistance. Relevant studies [20] show that nitric oxide (NO) signaling in podocytes is triggered by Ang II through angiotensin II type 2 receptor (AT2R). Abnormally elevated NO leads to podocyte hypertrophy and impairs the integrity of the glomerular filtration barrier.

3. Summary and Prospect

The pathogenesis of DN is complex and involves multiple biological processes. Mitochondrial dysfunction, inflammatory injury, oxidative stress and other key mechanisms play important roles in the development of DN. As an important component of the glomerular filtration barrier, podocyte injury is a key link in the occurrence and progression of glomerular diseases, as well as the pathophysiological basis leading to proteinuria, glomerulosclerosis and progressive deterioration of renal function. This paper summarizes the above relevant mechanisms and finds that these mechanisms interact and promote each other in complex processes, resulting in podocyte hypertrophy, foot process changes, reduction of podocyte number and volume, and ultimately progressive development of DN. In-depth understanding of the major regulatory factors in these mechanisms helps to identify new targets, promote the research and development of therapeutic drugs, and provide new therapeutic ideas for DKD.

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