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Progress of Chinese Medicine in Regulating Altered Lipid Metabolism in Renal Fibrosis

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Abstract: ***Renal fibrosis leads to progressive impairment of renal structure and function, which is a common pathologic impairment. There are few interventions targeting the mechanisms of fibrosis that can delay renal decompensation in patients. This review highlights the potential "antibiotic" of lipid metabolism and lipoproteins in ameliorating renal fibrosis, some representative targets and several other metabolic modulators with anti-fibrotic effects in the kidney, as well as the roles of fatty acid oxidation, lipids, and lipoprotein synthesis and catabolism in the prophylactic treatment of fibrosis. We describe the effects of lipid abnormalities on renal fibrosis and the renal pathophysiological lesions caused by lipid abnormalities, summarize the enzymes, transporter proteins, and transcription factors that contribute to the dysregulation of lipid metabolism in renal fibrosis, and discuss their roles in renal fibrosis. We summarized the renal protective effects of TCM monomers and TCM combinations mediating the pathways related to lipid metabolism flocculation, and made a review of them, aiming to provide theoretical basis for the drug development, basic research and clinical application of TCM in the prevention and treatment of renal fibrosis.***

Keywords: Renal fibrosis, Lipid metabolism, Lipoproteins, Fatty acid oxidation, Traditional Chinese medicine, Review**.**

1. Introduction

Fibrosis is an important pathological feature in the development of numerous diseases and can affect multiple organs such as the skin, eyes, lungs, kidneys, liver, and heart. Renal fibrosis is almost a common final pathological feature and outcome of all chronic kidney diseases. Currently, there are many pathogenesis mechanisms of renal fibrosis, such as lipid metabolism, oxidative stress, inflammation, signaling pathways, autophagy, and cellular senescence. Therefore, clarifying the pathogenesis of renal fibrosis, as well as the effective strategies and therapeutic targets for preventing and treating renal fibrosis, is of great significance for delaying the progression of kidney diseases. Renal fibrosis can alter the metabolism of lipids, lipoproteins, and fatty acids in the body, and these changes, in turn, can promote the further development of renal fibrosis. Therefore, we have reviewed the relevant content regarding how changes in lipid metabolism and lipoproteins lead to renal fibrosis and have introduced how they affect the process of renal fibrosis. At the same time, we have also conducted further research on how traditional Chinese medicine regulates lipid metabolism and lipoprotein-related pathways to alleviate fibrosis. Modern pharmacological studies have shown that traditional Chinese herbal medicines have unique advantages in the treatment of kidney diseases, such as multiple components, multiple pathways, high safety, and minimal adverse reactions. Therefore, this article explores the relevant pathways by which traditional Chinese medicine intervenes in lipid metabolism and lipoproteins, providing new ideas and strategies for the treatment of renal fibrosis.

2. Renal Fibrosis

Fibrosis usually occurs after tissue injury and is formed due to the excessive deposition of extracellular matrix components during tissue regeneration or wound healing [1]. It is not a static "scar", but a dynamic process, which specifically includes the following characteristics [2]: an increase in matrix production, inhibition of matrix degradation, regulation of matrix receptors to promote the interaction between cells and the matrix, the transformation from renal tubular epithelial cells to interstitial cells, processes related to monocytes, and apoptosis, etc [3, 4]. The key cellular mediators in fibrosis are myofibroblasts, which are mainly derived from fibroblasts [5]. Renal fibrosis is a common pathway in almost all chronic and progressive nephropathies and is characterized by massive proliferation of fibroblasts and excessive deposition of extracellular matrix, which in turn accelerates glomerulosclerosis [6]. The pathological changes of renal fibrosis can be divided into three main components, namely atherosclerosis and perivascular fibrosis in blood vessels, glomerulosclerosis, interstitial fibrosis, and. At the initial stage of mild injury, fibroblasts are able to coordinate tissue repair, allowing the fibrotic matrix to be absorbed, and at a later stage, as the injury progressively worsens, the organ structure and blood flow supply are disrupted, which leads to sclerosis of the renal parenchyma and the formation of fibrous scarring ultimately leading to renal failure [7].

3. The Influence of Lipid Metabolism on Renal Fibrosis

Lipid metabolism is a complex process involving multiple steps, including digestion, synthesis, degradation, and the transformation of lipids or lipid-containing structures within cells. Its main function is to distribute an appropriate amount of lipids throughout the body, thereby maintaining energy homeostasis [8]. Lipids have multiple functions in organismal and cellular physiology. For example, they play crucial roles in the composition of cell membranes, the storage and transportation of energy, as well as in signal transduction [9]. Under normal circumstances, lipids are stored in adipose tissue. However, excessive lipid accumulation can also occur in other tissues, such as the kidneys, liver, and muscles [10]. The disorder of lipid metabolism in the kidneys mainly stems from the disruption of three pathways: the uptake of fatty acids in the circulation, lipid synthesis, and lipid breakdown.

Accumulation of lipids in the renal tubules leads to renal fibrosis, with the tubulointerstitial region being the most susceptible to fibrosis [11]. In a rat model of diabetic nephropathy (DN), it was found that lipotoxicity resulting from lipid overaccumulation activates inflammatory and pro-fibrotic factors, which mediate podocyte dysfunction and apoptosis and ultimately lead to kidney injury [12]. Reduced lipolysis also induces an imbalance in renal lipid metabolism, and the key enzymes for triglyceride catabolism are hormone-sensitive lipase and triglyceride lipase, and up-regulation of the expression of hormone-sensitive lipase and triglyceride lipase in kidneys attenuates the accumulation of lipids in renal tubules [13].

3.1 The role of Fatty Acid Oxidation in Renal Fibrosis

Increased fatty acid binding proteins in fatty acid oxidation Fatty Acid Oxidation (FAO) expression leads to intracellular lipid accumulation resulting in renal fibrosis due to flocculation of lipid metabolism [14]. Studies have shown [15] that the formation of fibrosis is closely linked to the reduction of FAO. Impairment of the FAO pathway in renal tubular epithelial cells (TECs) during aging can lead to the accumulation of renal lipids which in turn leads to the development of renal fibrosis [16]. Although the kidney itself is not classified as a metabolic organ, TECs utilize FAO as the main source of energy and promote the body's metabolism through their reabsorption function. Inhibiting FAO in TECs can lead to ATP depletion, cell death, and the induction of cellular lipotoxicity, all of which may eventually progress to fibrosis. JIANG [17] performed a gene-wide transcriptomic study on a panel of normal and fibrotic human renal tubular samples and identified inflammation and metabolism as the predominant dysregulated pathways in renal disease. In particular, compared with the control group, both humans with tubulointerstitial fibrosis and mouse models exhibited lower expression levels of FAO regulators and key enzymes, along with higher intracellular lipid deposition, which was also confirmed by relevant in vitro experiments. From this, it can be inferred that restoring fatty acid metabolism through genetic or pharmacological methods can exert a renoprotective effect on mice. Peroxisome proliferator - activated receptors (PPARs) belong to the nuclear hormone receptor family. They exist in three different subtypes: PPARα, PPARβ, and PPARγ [18]. Together, they are involved in fatty acid oxidation, as well as glucose and lipid metabolism throughout the body. PPARα and PPARβ are highly expressed in oxidized tissues, and PPARα participates in the peroxisomal and mitochondrial FAO pathways through direct transcriptional control, which maintains lipid metabolism in metabolic organs, such as the liver and kidney. Relevant studies have shown that decreased expression of PPARα in renal tubular epithelial cells leads to inhibition of FAO. Targeting PPARα can ameliorate renal tubular epithelial injury and fibrosis in mice. Sian [19] et al, significantly reduced expression and inhibited PPARα activity in mouse TEC by aristolochic acid and ischemia-reperfusion in a mouse model of chronic kidney injury (AKI), which gradually resulted in FAO disorders, reduced ATP production, and accumulation of intracellular lipids, further suggesting that fatty acid oxidation is involved in the process of renal fibrosis. In addition, PPARγ agonists prevented interstitial fibrosis and inflammation in a unilateral ureteral obstruction (UUO) mouse model of renal fibrosis by decreasing renal Transforming growth factor-β (TGFβ) expression. Thus, a better understanding of fatty acid oxidation could help to further deepen the treatment of renal fibrosis.

3.2 TGF-β Signaling Pathway Intervenes in Renal Fibrosis by Regulating Lipid Metabolism

TGF-β is a major regulator of renal fibrosis, of which TGF-β1 is the most common isoform, and all three isoforms of TGF-β are central regulators of cellular differentiation, migration, proliferation, and gene expression [20]. TGF-β1 has been shown to convert TECs into extracellular matrix (ECM), give rise to fibroblasts or myofibroblasts, and induce epithelial to mesenchymal transition (EMT) [21]. Overexpression of active TGF-β1 has a pro-fibrotic effect [22].It has been previously shown that the TGF-β pathway, including the microRNA (miRNA) pathway, is an important component of its downstream signaling, and that TGF-β and miRNAs have coordinated roles with each other, with TGF-β regulating miRNA expression and miRNAs in turn regulating TGF-β. MiRNAs, which are non-coding RNAs consisting of approximately 23 nucleotides, are known to regulate the physiological and pathological processes in the kidney by regulating target gene expression to regulate renal physiopathological processes [23]. Among them, miR-21 is most abundantly expressed in the kidney and has the strongest correlation with renal pathogenesis [24]. miR-21 was the first miRNA shown to link lipid metabolism to renal fibrosis [25]. miR-21 inhibits PPAR-α expression by upregulating MiR-21 in DN rats, which disrupts lipid metabolism homeostasis, induces inflammation in ETCs accelerates the development of EMT in renal tissues and accelerates renal fibrosis by ECM deposition [26]. miR-21-5p inhibits TGF-β1 induced activation of Smad-2/3 to form a complex with smad4, producing a pro-fibrotic effect by antagonizing PPAR-γ. Similarly, SREBP1 and SREBP2 are major transcription factors that regulate fatty acid and cholesterol synthesis and promote DN fibrosis and inflammation via the TGF-β pathway [27]. These evidences above suggest that the TGF-β signaling pathway can induce miRNAs that are important for renal fibrosis by regulating lipid metabolism.

4. The Effect of Lipoproteins on Renal Fibrosis

Lipoproteins are composed of triglycerides, cholesterol, and an apolipoprotein B100 molecule, and abnormalities in lipoproteins exacerbate renal injury via the podocyte, and in animal models this podocyte injury radicalizes renal tubulointerstitial cell injury. Lipoproteins not only act as lipid carriers but also transport hormones, microRNA small molecule substances. Studies have shown that CKD patients', in addition to reduced levels of high-density lipoprotein (HDL) and cholesterol concentrations, are accompanied by altered lipoprotein composition, which aggravates the risk of cardiovascular disease and the progression of fibrosis in CKD patients [28]. Among the pro-fibrotic effects of cholesterol, Elena et al. found [29] that the proximal tubular epithelium is a target for lipid deposition in cholesterol-rich foods, where phospholipids in proximal tubular epithelial cells are increased in association with inflammation, fibrosis, and tubular injury. Peric et al. have demonstrated that feeding

male SD rats a diet containing 3-4% cholesterol leads to hypercholesterolemia

and is associated with aortic injury and glomerualar abnormalities, including glomerulosclerosis and interstitial fibrosis [30]. The antioxidant and anti-inflammatory functions of high-density lipoproteins (HDL) are essential to protect against lipid over-accumulation, maintain normal lipid metabolism and protect the kidney. However, HDL further prevents fibrosis formation by mediating reverse cholesterol transport needs further investigation [31].

5. Chinese Medicine Treats Renal Fibrosis by Improving Lipid Metabolism

There is no concept of "renal fibrosis" in Chinese medicine, but according to its etiology, pathogenesis, and clinical symptoms, it can be summarized as edema, Guan Ge, retention of urine, drowning toxicity, and lumbago, etc. [32]. It is similar to edema, oliguria, fatigue, sallow skin and other manifestations that appear in the end stage of renal fibrosis in modern medicine. In recent years, traditional Chinese medicine on renal fibrosis elaboration is mostly for this deficiency, this deficiency is mostly for the innate spleen and kidney insufficiency, acquired long illness, chronic disease, injury to the kidneys, renal yang insufficiency, the viscera lose warmth, the standard is mostly for the stasis, phlegm dampness, turbid toxin, when the positive deficiency and the evil real intertwined will be easy to cause phlegm and stagnation of each other, and the spleen deficiency can't transport the water and dampness, dampness and turbidity, and the accumulation of evil realities, and ultimately blocked the renal collaterals and veins, the formation of fibrosis. And "stasis" runs through the whole process of the disease, and blood stasis is common in CKD, so the treatment of activating blood circulation and removing blood stasis has a significant effect in the treatment of renal fibrosis. Chinese medicine believes that "prolonged illness will be stasis", "prolonged illness into the collateral", kidney disease for a long time, the deficiency of positive qi, qi deficiency and poor blood flow, and thus stasis, blocked in the collateral veins. In the progression of renal fibrosis, renal immune-mediated impairment of blood clotting function, all in the "internal knot for blood stasis" connotation [33]. Ma [34] et al. believe that renal fibrosis disease course extends over a long period of time, lipid peroxidation, lipid metabolism dysregulation of a wide range of appearances belong to the category of Chinese medicine turbid toxicity. Turbid toxicity stasis obstruction of renal channels, blood does not return to the menstruation caused by hematuria, turbid toxicity dark depletion of renal essence, essence does not transform blood, the essence of the long term loss of micro-regulation, become proteinuria and hypoproteinemia. The treatment should be warming the kidneys to drain turbidity, resolving blood stasis and detoxification method to regulate lipid metabolism and improve metabolism renal fibrosis. Lipoprotein belongs to the category of Chinese medicine, the pathogenesis of which is the weakness of the spleen and stomach, coupled with excessive consumption of fat, sweet and thick flavors produce phlegm and dampness in the body, poor qi and blood operation over time leads to blood stasis, accumulation in the kidney, damage to the kidneys. The treatment is to strengthen the spleen and resolve the dampness, lowering the fat and resolving the blood stasis so as to reduce the renal damage caused by lipoproteins [35]. In summary, it can be seen that turbidity and stasis runs through renal fibrosis, and at the same time, the treatment of turbid toxins and the method of removing stasis through Chinese medicine improves fibrosis and lays a solid theoretical foundation for its treatment.

5.1 Traditional Chinese Medicine Monomer

5.1.1 Berberine

Berberine (BBR), an isoquinoline alkaloid with a long history of medicinal application, is the major active constituent of Rhizoma coptidis and Cortex phellodendri [36]. BBR has multiple pharmacological activities, for example, lowering blood glucose, regulating blood lipids, antioxidant activity, anti-inflammatory activity, and increasing insulin sensitivity, and thus might represent therapeutic drug to treat DKD. BBR has anti fibrotic effect on kidney. It has been confirmed that cleavage can reduce lipid accumulation in TECs of DN mice, and improve mitochondrial morphology and membrane potential of kidney by increasing the expression of fatty acid oxidase acox1, CPT1 and PPAR-α in renal tubular epithelial cells of db / db mice [37].

5.1.2 Ergostane

Polyporus umbellatus is prepared from the dried sclerotia of Polyporus umbellatus Fries, Traditional medicine and contemporary pharmacological studies elucidated that Polyporus umbellatus had diuretic activity and was effective for treatment of some kinds of kidney diseases [38, 39]. Zhao et al [40] found that aristolochic acid I-induced attenuation of early renal tubular injury in SD rats by ergosterone inhibited the progression of interstitial fibrosis. It was found that ergosterone interfered with adenine-induced significant down-regulation of lipid levels and intrarenal protein expression of fibronectin, collagen type I and α-SMA in SD rats, further confirming that it could attenuate early renal tubular injury and enhance tubular excretory function to improve renal vascularization [41].

5.1.3 Baicalin

Baicalin, the main component found in the roots of the Baical skullcap, is a natural polyphenol that has been used in traditional Chinese medicine to treat inflammation, hypertension, bacterial and viral infections since ancient times. Lu [43] found that baicalin may have feedback in TGF-β/Smad signaling. SREBPs are transcription factors in lipid homeostasis, of which SREBP-1 is an important Smad3 coregulator of Smad3, which can be activated by TGF-β1. Smad3 was significantly reduced in nephritic tissues of STZ-induced DN rats after application of baicalin thus Inhibit the pathway of TGF-β1 and increase the degradation of cellular matrix to inhibit renal fibrosis [44].

5.1.4 Tripterygium Glycosides

Tripterygium glycosides are extracted and refined from celastrol plants in Celastraceae, which have anti-inflammatory, antioxidant and anti fibrotic effects [45]. Studies have confirmed that Tripterygium wilfordii

polyglycoside can regulate lipids and reduce renal damage, which is mainly through Tripterygium wilfordii polyglycoside inhibiting the expression of inflammatory factors (t NF - α and IL-6), reducing lipid deposition in glomerular basement membrane caused by lipid metabolism, and improving renal fibrosis [46].

5.1.5 Rhubarb

Rhubarb can prevent and treating CKD, and its pharmacological activity in alleviating renal dysfunction is closely associated with anthraquinone compounds. Rhubarb protects the kidney from fibrosis, oxidation, inflammation, autophagy, and apoptosis. Studies have shown that aloe emodin anti renal fibrosis, mainly through the regulation of 20 lipid metabolites screened by lipidomics, inhibits autophagy pi3k/akt/mtor pathway, activates cellular autophagy, and plays an anti renal fibrosis role [47].

6. Discuss

Disordered lipid metabolism and abnormal lipoprotein can lead to primary renal damage and aggravate renal fibrosis. Hypercholesterolemia often induces inflammation, ECM expression, fatty acid oxidation, changes in lipid and lipoprotein homeostasis, promotes macrophage phagocytosis, and blood lipids combine with extracellular matrix to affect renal vascular physiological status. Excessive lipid accumulation will increase cellular lipotoxicity, and lead to oxidative stress, endoplasmic reticulum reaction, mitochondrial function loss and other causes of renal fibrosis. Therefore, it is helpful to treat renal fibrosis by regulating the balance of FAO, lipid synthesis and decomposition, inhibiting tgf-β signaling pathway and related transcription factors to improve lipid metabolism disorders and reduce lipid accumulation. Although this article focuses on the description of lipid metabolism and lipoprotein abnormalities in the kidney, we cannot exclude the possibility that the abnormal renal lipid metabolism originated from other tissues. However, studies to identify anti fibrotic targets in this direction are still missing, and feasible therapeutic targets have not yet been found. Through consulting some clinical data, it is shown that traditional Chinese medicine does alleviate renal fibrosis and alleviate the damage of kidney disease. The above experimental study of traditional Chinese medicine monomer has significant curative effect in preventing and treating renal fibrosis by regulating lipid metabolism and lipoprotein to play a multi-target role. But its limitations also include the complex composition of traditional Chinese medicine, many active ingredients are unknown and difficult to analyze. These studies are mainly based on animal and cell models, lacking evidence from clinical evidence-based trials. Targeting lipid metabolism related enzymes FAO 、 Transporters, transcription factors, signaling pathways and so on have become good methods to treat fibrosis. Therefore, it is of great significance to treat and delay renal fibrosis by mining the targets and small molecule drugs related to lipid metabolism in the molecular regulation mechanism of renal fibrosis.

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