

Pathological Connections between Nonalcoholic Fatty Liver Disease and Chronic Kidney Disease

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Keywords

Nonalcoholic fatty liver disease · Chronic kidney disease · Pathogenic mechanisms · Interaction · Common pathway

Abstract

Background: Nonalcoholic fatty liver disease and chronic kidney disease are major public health issues worldwide. The clinical burden of nonalcoholic fatty liver disease is not only confined to liver-related morbidity and mortality, but it also includes the burden of chronic extrahepatic complications. It is well known that liver and kidney are strictly interconnected in physiological and pathological conditions. **Summary:** Mounting evidence indicates a strong association between nonalcoholic fatty liver disease and chronic kidney disease, independent of the identified cardiorenal risk factors. The presence and severity of nonalcoholic fatty liver disease are related to the developmental stage and risk of chronic kidney disease. And chronic kidney disease progression also contributes to nonalcoholic fatty liver disease development. Nonalcoholic fatty liver disease and chronic kidney disease mutually contribute to disease progression through pathological links. Shared pathogenic mechanisms also exist between nonalcoholic fatty liver disease and chronic kidney disease, including pyroptosis and ferroptosis.

Additionally, the use of combined liver-kidney transplantation has increased exponentially in recent years. **Key Messages:** This review focuses on the emerging pathological mechanisms linking nonalcoholic fatty liver disease and chronic kidney disease and shared pathogenic mechanisms to find novel targeted therapies and retard the progression of both disease processes.

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Published by S. Karger AG, Basel

Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as the accumulation of fat (>5%) in hepatocytes in the absence of excessive alcohol consumption or other causes of liver disease, including autoimmune hepatitis, drug-induced hepatitis, and viral hepatitis [1]. NAFLD is a spectrum of liver disorders ranging from simple steatosis, nonalcoholic steatohepatitis, fibrosis, to hepatocellular carcinoma [2]. NAFLD is currently considered a liver manifestation for metabolic syndrome and multisystem conditions [3]. In NAFLD, the key physiological functions of the liver, including glucose and lipid metabolism, are disturbed; thus, the pathophysiological effects of NAFLD extend beyond the liver. NAFLD has evolved

from a relatively unknown disorder to the most common chronic liver disease, substituting for viral hepatitis over the past 20 years, affecting up to 25–30% of the population worldwide [4]. CKD is defined as a glomerular filtration rate of <60 mL/min/1.73 m², albuminuria of ≥30 mg per 24 h, or persistence of renal impairment markers for >3 months, regardless of the cause [5]. CKD is an important public health problem, which causes substantial global morbidity and increases all-cause mortality, affecting 8–16% of the population worldwide [6]. A significant proportion of patients develop end-stage renal disease or CVD, despite receiving standard treatment for CKD, and the all-cause mortality remains unchanged. These findings suggest that current therapies do not affect the critical pathogenic mechanisms contributing to CKD progression [7].

A growing body of evidence reveals the strong association between NAFLD and CKD. Several cross-sectional studies have demonstrated that in patients with NAFLD, the morbidity of CKD is 20–55% compared with 5–30% among patients without NAFLD [8, 9]. Besides, a cohort study over a follow-up of 6.5 years, the Valpolicella Heart Diabetes Study by Targher et al. [10] revealed that the presence of NAFLD on ultrasonography was associated with an approximately 50% increased risk of incident CKD. Moreover, a meta-analysis of 20 cross-sectional studies (involving approximately 30,000 individuals) showed that NAFLD was associated with a two-fold increase in the prevalence of CKD. Data from 13 longitudinal studies (involving approximately 28,500 individuals) demonstrated that NAFLD was associated with an approximately 80% increased risk of CKD development [8]. The largest and most updated meta-analysis to date by Mantovani et al. [11] found that NAFLD increased the risk of incident CKD by almost 40% over a long-term follow-up. But it is unclear whether there is a causal relationship between NAFLD and CKD. Moreover, NAFLD and CKD share common pathways, including pyroptosis and ferroptosis. In this review article, we provide comprehensive understanding of emerging pathogenic mechanisms between NAFLD and CKD to assist with the management of these patients.

Pathological Connections between NAFLD and CKD

Fructose and Vitamin D

Cumulative evidence suggests that enhanced fructose intake is associated with the incidence and severity of NAFLD and CKD [12]. Fructose (70%) is phosphorylated

in the liver to generate fructose-1-phosphate, eventually leading to the accumulation of uric acid. A cross-sectional study revealed a high prevalence of hyperuricemia in patients with CKD and NAFLD [13]. Uric acid promotes the progression of NAFLD and CKD through adenosine-triphosphate (ATP) depletion; inhibits endothelial NO synthase; increases intracellular oxidative stress, mitochondrial injury, endothelial injury, and RAS activation; and enhances hepatic, renal lipogenesis and the secondary inflammatory response [14–19]. Experimental studies have shown that uric acid-lowering agents improve fructose-induced NAFLD and CKD [18, 20].

Vitamin D deficiency and insufficiency are common among patients with CKD or undergoing dialysis and often reported in people with chronic liver diseases [21]. NAFLD and CKD are characterized by vitamin D resistance, which is in part due to impaired hepatic 25 hydroxylation and reduction in renal 1,25[OH]₂D₃ production [7]. Furthermore, several observational and experimental studies have revealed that vitamin D deficiency is related to the pathogenesis and severity of NAFLD and CKD [22]. First, vitamin D can alleviate liver inflammation and oxidative stress by inhibiting the p53–p21 signaling pathway, reducing cell senescence, and reducing fatty liver by promoting the nuclear translocation of the antioxidant molecule nuclear factor erythroid 2-related factor 2, thereby decreasing toll-like receptor levels or restraining sirtuin [23]. Animal models of hepatic IR and hepatic steatosis can be improved by the activation of hepatocyte nuclear factor 4α mediated by the vitamin D receptor [24]. Second, vitamin D deficiency and low expression of vitamin D receptor exacerbate the inflammatory response [25]. Third, adipose tissue (AT) is also a major target of vitamin D action, where vitamin D modulates insulin sensitivity, local inflammation, and adipokine secretion. Vitamin D ameliorates AT inflammation and prevents hepatic steatosis by reducing lipid droplets for AT export and hepatic de novo lipogenesis and fatty acid oxidation.

Lipid Disorders

NAFLD is characterized by exaggerated lipid accumulation, and dyslipidemia and release of pro-inflammatory cytokines are considered to play an important role in the pathological progression of CKD [26]. There is increasing evidence to suggest that ectopic lipid deposition plays a key role in accelerating the progression of NAFLD and CKD [27]. Dysregulation of lipid homeostasis can generate excess free fatty acids in the circulation, which in turn increases the mitochondrial inner membrane permeability, resulting in the loss of membrane potential and ATP

synthesis ability and eventually causing mitochondrial dysfunction and potentially a systemic inflammatory response [28, 29]. Lipotoxicity causes excessive ROS production in the liver, which is an important mediator of damage to glomerular epithelial cells and promotes the expression of pro-fibrotic molecules such as transforming growth factor beta 1, thereby promoting fibrosis of the kidney [30]. In addition, lipid disorder can induce endoplasmic reticulum stress and activate pro-inflammatory pathways converging on the NF- κ B and c-Jun-N-terminal kinase pathways in hepatocytes, thereby accelerating the progression of CKD [31, 32]. Lipid excess can also play a central role in IR, which is a typical pathogenic factor of NAFLD and CKD [33].

Insulin Resistance

IR is an early metabolic alteration in CKD patients, being apparent when the glomerular filtration rate remains within the normal range and being almost universal in patients reaching the end-stage renal failure. And IR is the major mechanism in the development and progression of NAFLD [34, 35]. Excessive lipid deposition can result in excessive free fatty acids in the circulation, as well as an increase in the release of pro-inflammatory cytokines, leading to systemic IR. Animal studies have revealed that the progression of NAFLD can further aggravate IR and result in atherogenic dyslipidemia and inflammatory cytokine release, both of which can contribute to CKD. IR due to visceral adiposity and metabolic dysregulation can induce systemic chronic inflammation, subsequently causing systemic endothelial dysfunction, which can accelerate the course of CKD [36]. IR can also induce endoplasmic reticulum stress and very-low-density lipoprotein, leading to podocyte cell death in glomeruli [32].

Genetic Predisposition

Accumulating data support a genetic link between NAFLD and CKD, mostly sustained by the major NAFLD risk polymorphisms [37]. Emerging studies suggest that genetic polymorphisms in PNPLA3, HSD17B13, TM6SF2, MBOAT7, and GCKR are important in the development of NAFLD. Several NAFLD-associated genetic polymorphisms have also been associated with CKD [38]. The protein encoded by the PNPLA3 shows lipase activity against triglycerides and retinyl esters, which is highly expressed in the podocytes, tubular cells, adipocytes, hepatocytes, hepatic stellate cells, and other cells [39]. The PNPLA3 rs738409C > G variant encoding an isoleucine-to-methionine substitution at amino acid position 148 (I148M) impairs the activity of triglyceride and

retinyl-palmitate lipase and increases the levels of triglycerides and retinyl esters, contributing to NAFLD [40]. A meta-analysis of 23 case-control studies found that PNPLA3 rs738409C > G polymorphism was associated with NAFLD and NASH [41]. However, some studies have shown that patients with the PNPLA3 variant are more susceptible to poor kidney function, independent of age, sex, adiposity, hypertension, diabetes, and NAFLD severity [42, 43]. It has been speculated that expression of the PNPLA3 variant stimulates renal ectopic lipid deposition, resulting in glomerulosclerosis and renal tubular injury, and further leads to the decline of renal function [44]. What is more, HSD17B13 variant rs72613567 may be protective against NAFLD by affecting hepatic fat metabolism [45]. A 2020 study revealed that HSD17B13 variant carriers showed higher estimated glomerular filtration rate (eGFR) levels than homozygous subjects independent of NAFLD [37].

In addition, the rs58542926 variant of TM6SF2 has been reported to promote NAFLD by regulating hepatic triglyceride secretion [46, 47]. Musso et al. [48] found that the T allele of the TM6SF2 gene was associated with a higher eGFR and lower prevalence of microalbuminuria, which may be beneficial to the kidney. The rs641738 variant of MBOAT7 is related to the increased risk of NAFLD [49]. And MBOAT7 variant is associated with worse CKD stages in a cohort of patients with biopsy-proven NAFLD [50]. The T allele of GCKR rs1260326 is associated with increased risk of NAFLD, possibly through enhanced hepatic de novo lipogenesis [51]. At the same time, the GCKR variant may increase the risk of CKD [52]. However, it remains uncertain as the available data are contradictory. For example, some studies have associated variants with higher risk of CKD, and some have associated higher eGFR [53].

Molecular Sensor and Platelet Activation

In mammals, cellular metabolism is orchestrated by molecular sensors of energy, nutrient, and oxygen status to adapt to changing substrate availability. Dysregulation of related molecular sensors, including 5'-AMP-activated protein kinase, hypoxia-inducible factor-1 α , and mammalian target of rapamycin (mTOR), has been implicated in the pathogenesis of NAFLD and CKD [7]. The energy sensor 5'-AMP-activated protein kinase is the key point directing hepatocytes and podocytes to compensatory and potentially deleterious pathways, which lead to inflammatory and pro-fibrotic cascades and ultimately end-organ damage. Hypoxia-inducible factor-1 α , following stimuli such as chronic intermittent hypoxia and lip-

id excess, contributes to the developmental progression of NAFLD, and chronic hypoxia is implicated in kidney damage resulting from early diabetes and obesity-associated CKD [54, 55]. The nutrient sensor mTOR can form two types of molecular complexes: mTOR complex 1 and mTOR complex 2. Inappropriate activation of mTOR complex 1 mTORC1 inhibits autophagy and promotes IR, ectopic lipid accumulation, lipotoxicity, and recruitment of pro-inflammatory monocytes, thus accelerating the progression of NAFLD and CKD [56, 57]. In addition, dyslipidemia and increased oxidative stress are key features of NAFLD and CKD, whereas both increased oxidative stress and triglyceride-rich lipoproteins are pivotal regulators of platelet activation [58, 59]. When activated, platelets release a variety of pro-inflammatory cytokines, chemokines, and growth factors, such as chemokine (CXC motif) ligand 4, serotonin, transforming growth factor (TGF)-beta, and platelet-derived growth factor, all of which can activate stellate cells to increase the production of extracellular matrix, leading to liver disease progression [8]. Indeed, patients with CKD have increased platelet activation and attenuated response to dual anti-platelet therapy compared with non-CKD patients.

Gut Dysbiosis

The gut microbiota dysbiosis is a hallmark of NAFLD, and the signatures of gut microbiota are associated with the disease severity by altering bacterial metabolites [60]. Accumulating evidence suggests that the gut microbiota plays an important role in the development of hypertension and CKD [61]. Gut dysbiosis, including altered microbial metabolism and disrupted intestinal barrier integrity, has been shown to be related to the severity of chronic diseases of the liver and kidney [62]. The gut microbiota composition is altered in patients with NAFLD and CKD, and the healthy Bacteroidetes, Lactobacillaceae, and Prevotellaceae families are relatively reduced [63]. CKD itself may induce intestinal disorders and systemic inflammation, thereby promoting NAFLD. CKD is characterized by the accumulation of uremic toxic metabolites due to a decrease in renal clearance, such as urea, indoxyl sulfate, p-cresyl sulfate, and trimethyl-amine-N-oxide (TMAO) [64]. Urea is hydrolyzed in the gastrointestinal lumen by microbial urease to ammonia and then converted to ammonium hydroxide, which can damage the tight junctions of the intestinal epithelium [65]. The liver cytochrome P450 enzyme is directly affected by indoxyl sulfate, and TMAO causes liver toxicity [66, 67]. A cohort study found that plasma TMAO levels were higher in patients with CKD than in healthy controls while

plasma TMAO levels are also elevated in patients with NAFLD and are associated with higher serum bile acid concentrations [66, 67]. Certain species in the gut microbiota produce short-chain fatty acids, such as butyrate, acetate, and propionate, which disrupt the integrity of the gut barrier and exert systemic effects through diffusion across the gut mucosa [68].

The intestinal barrier is disrupted, resulting in the leakage of endotoxin or bacterial DNA from the circulation and thereby leading to the activation of pattern recognition receptor-mediated immune cells and the release of pro-inflammatory cytokines in the circulation, which contribute to liver or kidney injury. Progression of CKD and NAFLD may further affect intestinal barrier function [65].

Activation of RAS

In addition to adipocytes, the kidney and liver also express RAS components, and experimental studies support both systemic and local activation of AngII in NAFLD and CKD [69]. The activation of RAS is considered to play a key role in the pathogenesis of NAFLD and CKD [69]. In the kidney, RAS activation triggers renal ectopic lipid deposition, which is known to cause oxidative stress and inflammation through hemodynamic effects of glomerular efferent arteriole vasoconstriction leading to glomerulosclerosis. Furthermore, in the liver, AngII promotes IR, de novo lipogenesis, mitochondrial dysfunction, ROS, and pro-inflammatory cytokine production and activates hepatic stellate cells to induce fibrogenesis, thus contributing to the progression of NAFLD [70]. Blocking RAS system can attenuate fibrosis in NAFLD and CKD.

Common Pathogenic Mechanisms

Pyroptosis

Pyroptosis, the most recently described form of programmed cell death, is downstream of inflammasome activation. Pyroptosis can be activated by canonical and noncanonical signaling pathways. The canonical pathway begins with inflammasomes that recognize pathogen-associated molecular patterns and damage-associated molecular patterns. The noncanonical pathway relies on caspase-11, which can function independently of inflammasomes [71]. In addition, the activation of pyroptosis can also be divided into gasdermin D (GSDMD)-dependent pathway regulated by caspases 1/4/5/11 and GSDME-dependent pathway regulated by caspase 3 [72].

NAFLD is closely related to glycolipid metabolism and liver inflammation. Nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome can be activated by many danger factors in hepatocyte, finally triggering pyroptosis and inflammatory cascade. And the NLRP3-caspase-1-GSDMD signaling pathway is the key mechanism of kidney cell pyroptosis in CKD. Therefore, pyroptosis has been implicated as a common pathway in NAFLD and CKD.

Pyroptosis is thought to play an important role in the development and progression of NAFLD because low-grade chronic inflammation in the liver is a universal hypothesis in the pathophysiology of NAFLD. Increasing evidence has identified that release of inflammasome particles, especially NLRP3 inflammasome, and subsequent hepatocyte pyroptosis contribute to the progression of NASH in both human and animal models [73]. And pyroptosis leads to the release of NLRP3 inflammasome from hepatocytes into the extracellular space, where they are taken up by other cells and mediate inflammatory and pro-fibrogenic stress signals [73]. Xu et al. [74] revealed that GSDMD plays a key role in the pathogenesis of NASH by regulating lipogenesis, the inflammatory response, and the NF- κ B signaling pathway. Pro-inflammatory cytokines released during pyroptosis are key molecules in the development of NAFLD, including interleukin (IL)-1 β , IL-18, ATP, and high mobility group box-1. Ezquerro S et al. [75] proposed that in the IR state, hepatic high mobility group box-1 expression and secretion are altered, thereby contributing to the progression of NAFLD to NASH by activating hepatocyte pyroptosis. The activation of IL-1 signaling downstream of inflammasomes has been implicated in the pathogenesis of NAFLD [76]. Therefore, pyroptosis exerts an important role in stages of NAFLD progression.

Kidney diseases are characterized by progressive destruction of renal function by sustained inflammation. Pyroptosis is a key fibrotic mechanism that is critical in the development of kidney pathology [77]. Studies have found that pyroptosis can exist and develop in various CKDs, such as DKD, renal fibrosis, and obstructive nephropathy. The NLRP3-caspase-1-GSDMD signaling pathway is also the main mechanism of kidney cell pyroptosis in CKD [78]. What is more, Komada et al. [79] found that during the course of CKD, damage-associated molecular patterns can activate AIM2 inflammasome in macrophages, which leads to pyroptosis, and promoted inflammation to accelerate fibrosis. Lipopolysaccharide can activate caspase-11 through the noncanonical pathway when pathogens invade renal cells, and Yang et al.

[80] found that ischemia reperfusion can also induce caspase-11 activation in mouse renal tubular epithelial cells. And caspase-11 knockout mice can have reduced pyroptosis-related protein production and the release of inflammatory factors in renal tubular epithelial cells, slowing the progression of CKD [81]. Therefore, pyroptosis, as a common pathogenic mechanism in NAFLD and CKD, could serve as a potential therapeutic option for both diseases.

Ferroptosis

Ferroptosis is a new kind of regulated cell death that is characterized by highly iron-dependent lipid peroxidation. It is generally accepted that ferroptosis has three basic features, including amount of available iron and loss of lipid peroxidation repair capacity and glutathione peroxidase 4 (GPX4) activity. Iron overload and oxidative stress are major triggers that contribute to liver injury and disease progression in most liver diseases and ferroptosis can aggravate liver damage in NAFLD [82]. Most patients with CKD exhibit varying degrees of iron metabolism and lipid metabolism disorders. Loguercio et al. [83] observed that more than 90% of NAFLD patients in their study exhibited elevated levels of lipid peroxidation markers (malondialdehyde and 4-hydroxynonenal). Qi et al. [84] showed that ferroptosis affects NASH via regulating lipid peroxidation-mediated cell death in mice. It has been confirmed that enolase 3 promoted NASH progression by negatively regulating ferroptosis via upregulating GPX4 expression and lipid accumulation [85]. Through both in vivo and in vitro assays, Tsurusaki et al. suggested that NaAsO₂ can lead to ferroptotic cell death further inducing NASH. Ferroptosis can be regulated by the nuclear factor E2-related factor 2 (Nrf2)-mediated antioxidant response. Nrf2 can upregulate the expression of downstream heme oxygenase-1, glutathione (γ -glutamylcysteinylglycine, GSH), and GPX4, thus eliminating ROS accumulation and reducing malondialdehyde levels in the liver [86]. And activation of the Nrf2 pathway significantly ameliorates in NAFLD mice model [87]. However, the role played by ferroptosis at various stages of NAFLD progression warrants further investigation and exploration.

Current studies suggest that ferroptosis is related to the pathogenesis of acute renal injury. However, ferroptosis may be very important in the progression of acute renal injury-CKD through lipid peroxidation and GPX4 activity [79]. Renal iron deposition can be seen in different CKD syndromes [88]. Renal iron deposition occurs spontaneously in different types of CKD in the absence of exogenous iron supplementation and is associated with

ischemia-, hypoxia-, and cytotoxicity-induced release of catalytic iron [89–91]. This suggests that CKD renal iron accumulation initially induces ferroptosis. Many patients with CKD exhibit varying degrees of disorders of iron deposition and ectopic lipid sedimentation, which provides a favorable condition for ferroptosis, and oxidative stress boosts lipid peroxidation. However, experimental studies involving CKD and ferroptosis induced by different pathological factors are still lacking [92]. The ferroptosis pathway is considerable, and its molecular network is complex. As the common pathogenic mechanisms of NAFLD and CKD, its role and mechanism with both diseases requires further clarification.

Conclusion

The incidence and prevalence of NAFLD and CKD are increasing annually, and both diseases have become major public health burdens worldwide. Accumulating evidence suggests that both diseases are increasingly linked and influenced mutually. Moreover, there are common pathogenic pathways between NAFLD and CKD. The emerging pathogenic mechanisms linking NAFLD and CKD are thought to be manifold. NAFLD is an important risk factor for CKD while CKD can also promote the progression of NAFLD. Both mutually promote each other through multiple mechanisms, including alterations in nutrient-related fructose and vitamin D, lipid overload, and IR. Additionally, genetic predisposition, molecular

sensors, and intestinal dysfunction and activation of the RAS exert important roles. Shared pathogenic pathways include pyroptosis and ferroptosis. However, the current findings remain inconclusive regarding whether there is a causal relationship between NAFLD and CKD. Although NAFLD and the stages of CKD are related, the correlation of NAFLD with the pathological type of CKD remains unclear. In conclusion, we have meticulously elaborated on the novel tight pathogenesis for NAFLD and CKD to provide a basis for better management of these patients. However, further studies are required regarding the causal relationship between both diseases and the effects of different pathological types of CKD.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This research was funded by the National Natural Science Foundation of China (grant number: 81770736).

Author Contributions

Huixia Liu and Jing Xiong conceived and designed the work; Chun Zhang reviewed and edited the work. All authors were involved in drafting and revising the manuscript.

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