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Review Article

Influence of Nonalcoholic Fatty Liver Disease on the Occurrence and Severity of Chronic Kidney Disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is reported to affect 20-30% of adults and is accompanied by various metabolic comorbidities, where the economic and clinical burden of NAFLD is attributed to the progression of liver disease as well as the presence of extrahepatic diseases. Chronic kidney disease (CKD), which has a high incidence rate, high morbidity and mortality rates, and high medical costs, has been linked to NAFLD. CKD is associated with some metabolism-related risk factors that overlap with metabolic comorbidities of NAFLD. Therefore, to investigate the potential factors that influence CKD occurrence, the association between NAFLD and CKD should be clarified. Some studies have confirmed that NAFLD influences the occurrence and severity of CKD, whereas some studies have indicated that there is no correlation. In this review, the results of a few studies have been discussed, the potential risk factors for CKD in NAFLD are explored, and the respective biological mechanisms are elaborated to help clinicians identify CKD in patients much earlier than it is diagnosed now and thus help in reducing the incidence of liver and kidney transplants.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) includes different types of liver damage, ranging from simple steatosis and nonalcoholic steatohepatitis (NASH) to liver cirrhosis and even hepatocellular carcinoma.[1,2] NAFLD is diagnosed by the presence of more than 5% fat accumulation in liver cells after excluding excessive alcohol intake in patients as well as other secondary causes of liver disease, such as drug-induced liver injury, viral and autoimmune hepatitis.[3] The prevalence of NAFLD is reported to be 20–30% among the adult population in western countries.[4] Due to the variety of metabolic comorbidities it accompanies, such as hypertension, insulin resistance, diabetes mellitus (DM), dyslipidemia, and central obesity, international experts decided to change its name to metabolic dysfunction-associated fatty liver disease (MAFLD).[5] NAFLD is also reported to increase the risk of cardiovascular disease in patients.[6] Thus, the economic and clinical burdens of NAFLD are not only associated with the progression of liver disease but also with various extrahepatic diseases.[7]

The diagnostic criteria for chronic kidney disease (CKD) are either the reduced estimated glomerular filtration rate (eGFR) (<60 mL/min/1.73^2) and/or abnormal albuminuria and/or overt proteinuria in patients for at least 3 months.[8] In western countries, more than 25% of people aged >65 years are affected with CKD.[9] CKD is a major risk factor for cardiovascular disease and end-stage kidney disease. It is a serious health threat that is associated with high morbidity and mortality rates and high medical costs.[10] Therefore, investigating the potential influencing factors of CKD is essential to helping clinicians in their early intervention efforts for the disease. Reportedly, hypertension, dyslipidemia, obesity, and insulin resistance are considered risk factors for CKD that overlap with the metabolic comorbidities of NAFLD.[11]

The association between NAFLD and CKD has recently attracted the attention of many experts. NAFLD and CKD share some common pathophysiological mechanisms as well as some metabolic risk factors for cardiovascular disease.[12,13] Some studies have confirmed that the presence of NAFLD increases the risk of CKD and that the degree of liver fibrosis is related to CKD stage,[14,15] while other studies have found that the incidence of CKD is not affected by NAFLD.[16] In addition, hepatorenal syndromes in patients with decompensated cirrhosis confirm the pathophysiological relationships between the liver and kidney.[17] In this article, we have reviewed the results of studies on the relationship between NAFLD and CKD, explored the potential risk factors for CKD in NAFLD patients, and elaborated on the possible mechanisms in order to explore the possibilities of early intervention for CKD. All the data from this review are presented in Tables 1 and 2.[14–16,18–43]

Renal function markers in NAFLD patients

Changes in different markers reflecting renal function, such

Keywords: Non-alcoholic fatty liver disease; Chronic kidney disease; Review; Risk factors.

Abbreviations: BUN, blood urea nitrogen; CI, confidence interval; CKD, chronic kidney disease; Cr, creatinine; DM, diabetes mellitus; FLI, fatty liver index; eGFR, estimated glomerular filtration rate; aHR, adjusted hazard ratio; HR, hazard ratio; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OR, odds ratio; RAAS, renin–angiotensin–aldosterone system.

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Table 1. Data of meta-analyses included in this review

Author, year	Included studies, *n*	NAFLD patients, *n*	CKD diagnosis, *n*	Main findings
Zou *et al*., 2020[26]	6	21,450	1,211	Pooled incidence of CKD among NAFLD was 9.2 per 1,000 person-years (95% CI: 5.7–14.6, $p<0.01$; $I^2=96.2\%$)
Mantovani *et al*., 2018[31]	9	32,898	4,653	NAFLD increased the risk of CKD (HR: 1.37, 95% CI: 1.20–1.53, $p<0.0001$; $I^2=33.5\%$); the more severe the NAFLD, the higher the risk of developing CKD (HR: 1.50, 95% CI: 1.25–1.74, $p<0.0001$; $I^2=0\%$)
Musso *et al*., 2014[34]	33	–	–	NAFLD increased the risk of CKD (HR: 1.79, 95% CI: 1.65–1.95, $p<0.00001$). NASH and advanced fibrosis was associated with a higher incidence of CKD (HR: 2.12, 95% CI: 1.42–3.17, $p=0.0002$; HR: 3.29, 95% CI: 2.30–4.71, $p<0.0001$, respectively)

CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

as the levels of eGFR, creatinine (Cr) and blood urea nitrogen (BUN), the incidence of proteinuria, and urinary albumin-to-creatinine ratio levels in NAFLD patients were studied. Patients who had NAFLD showed lower eGFR than those without NAFLD (91±32 vs. 96±31 mL min^{-1} 1.73 m^{-2}, $p=0.001$),[18] a higher incidence of proteinuria (36.4 vs. 4.4%, $p<0.0001$),[19] and higher albumin-to-creatinine ratio levels (13.4±27.6 vs. 3.1±9.9 mmol/mol, $p<0.0001$).[20] Other studies have also supported these results.[21,44] However, no difference was reported in baseline Cr and BUN levels in patients with and without NAFLD.[22,23] We hence hypothesized that Cr and BUN levels may not be the most sensitive indicators of early renal function impairment. However, Choudhary *et al*.[24] demonstrated no difference in eGFR or Cr levels nor the incidence of proteinuria between individuals with biopsy-confirmed NAFLD and patients with normal liver histology. Therefore, to evaluate the effect of NAFLD on renal function, further studies are required.

Associations between presence of NAFLD and risk of CKD

Because NAFLD is usually accompanied by multiple metabolic comorbidities, and CKD is also affected by multiple metabolic factors, it is difficult to accurately infer their relationship. DM is a systemic disease that is closely associated with NAFLD and CKD. Studies have shown that 40–69% of DM patients develop NAFLD, and the latter is associated with poor glycemic control in DM.[45,46] Meanwhile, NAFLD has also been well-demonstrated to increase the risk of DM.[47] Additionally, DM is considered a cause of CKD and is reported to significantly increase the risk of CKD occurrence.[48,49] To investigate the relationship between NAFLD and CKD, it is important to exclude the interference of DM.

Targher *et al*.[18–20,25] reported that the presence of NAFLD was associated with an increased risk of CKD in both type 1 and type 2 diabetes patients and was not affected by such baseline data as body mass index, waist circumference, blood pressure, blood lipids, and glycosylated hemoglobin. Ahn *et al*.[22] reported that NAFLD could increase the incidence of CKD by 1.68 times (95% confidence interval [CI]: 1.27–2.24), after being classified by hypertension and DM. Zou *et al*.[26] conducted a meta-analysis involving 20,030 individuals and found that the pooled overall prevalence of CKD among NAFLD patients was 9.2 per 1,000 person-years, which when combined with the occurrence of type 1 or 2 diabetes, was observed to increase significantly (63.0 per 1,000 person-years). However, whether the presence of diabetes is associated with an increased all-cause mortality rate is unclear; more attention should be paid to the low quality of these patient's lives and the benefits that they can reap from a hypoglycemic agent.

Hypertension, a component of metabolic syndrome, has been reported in multiple studies to increase the risk of NAFLD, independent of the obesity factor, with an estimate of 50% of patients with hypertension having NAFLD.[50–53] Hypertension, as a cause for CKD, is usually primary, has a longer history than CKD, and is often accompanied by hypertensive target organ damage. A decrease in eGFR often precedes the onset of renal tubular concentrating dysfunction. Hypertension increases the production of angiotensin II by activating the renin-angiotensin-aldosterone system (RAAS), which reduces renal perfusion through the constriction of renal vessels, induces renal hyperfiltration (caused by the discordant degree of afferent and efferent arterioles contraction), and then leads to glomerulosclerosis and tubule-interstitial inflammation, ultimately leading to CKD.[54,55] Hypertension caused by CKD is secondary and is attributed to various renal parenchyma and vascular lesions through the mechanisms of activation of the RAAS, the sympathetic nervous system, water and sodium retention, and endothelial dysfunction. The incidence of hypertension varies from 60% to 90% in different CKD stages.[56,57] These findings indicate that exclusion of the interference of hypertension is important. No association between liver fat and CKD was reported in the Framingham Heart Study, after adjusting for blood pressure, blood lipids, DM, and other covariates.[27] This study adjusted the use of drugs such as antihypertensive drugs and aspirin, suggesting that the two diseases may be linked by their common risk factors.

Sirota *et al*.[16] reported that ultrasound-diagnosed NAFLD was not associated with CKD occurrence in American adults after adjusting for the characteristics of metabolic syndrome. Based on this result, Zhang *et al*.[28] revealed the origin of discrepancy between eastern and western patients with respect to the relationship between NAFLD and CKD. NAFLD was an independent risk factor for CKD in the Chinese cohort; however, no such results were found in the USA cohort. The subgroup analysis found that NAFLD was associated with early stages of CKD but not with the later stages (in both groups); therefore, negative relationships were reported in the USA cohort, which mainly consisted of advanced CKD patients.

Some studies have shown that the severity of NAFLD correlates with the CKD risk.[29] In a retrospective cohort study, patients with NAFLD showed an increased incidence of CKD by 41%. After adjusting for confounders, NAFLD was found to be a significant risk factor for CKD (adjusted hazard ratio [aHR]=1.58, 95% CI: 1.52–1.66), where the presence of cirrhosis increased the CKD risk (compensated cirrhosis:

Table 2. Main findings of the included studies about relationships between NAFLD and CKD

Author, year	Study design	Diagnostic method for NAFLD	Diagnostic method for CKD	Sample size and rate of NAFLD	CKD incidence, *n*	Main findings
Xu *et al*., 2016[14]	Cross-sectional study	Ultrasonography	eGFR <60 mL/min/1.73 m^2	755, 100%	61	FIB-4 score ≥1.100 (OR: 2.660, 95% CI: 1.201–5.889, p=0.016), were independent predictors of CKD among NAFLD patients
Targher *et al*., 2014[15]	Retrospective, longitudinal cohort study	Ultrasonography	eGFR <60 mL/min/1.73 m^2 and/or macroalbuminuria	261, 50.2%	61	NAFLD increased the risk of CKD (aHR: 2.03, 95% CI: 1.10–3.77, p<0.01) in patients with type 1 diabetes
Sirota *et al*., 2012[16]	Cross-sectional study	Ultrasonography	eGFR <60 mL/min/1.73 m^2 or the presence of albuminuria	11,469, 36%	2,891	NAFLD was not associated with the occurrence of CKD (OR=1.04, 95% CI: 0.88–1.23, p=0.64)
Targher *et al*., 2008[25]	Prospective cohort study	Ultrasonography	Overt proteinuria and/or eGFR <60 mL/min/1.73 m^2	1,760, 73%	547	NAFLD increased the risk of CKD (aHR: 1.49, 95% CI: 1.10–2.20, p<0.01) in patients with type 2 diabetes
Targher *et al*., 2008[18]	Cross-sectional study	Ultrasonography	Overt proteinuria and/or eGFR ≤ 60 mL/min/1.73 m^2	2,103, 67%	284	NAFLD increased the risk of CKD (OR: 1.87, 95% CI: 1.30–4.10, p=0.02) in patients with type 2 diabetes
Targher *et al*., 2010[19]	Cross-sectional study	Ultrasonography	Abnormal albuminuria or eGFR ≤60 mL/min/1.73 m^2	202, 54.9%	51	NAFLD increased the risk of CKD (aOR: 3.90, 95% CI: 1.50–10.10, p=0.005) in patients with type 1 diabetes
Targher *et al*., 2012[20]	Cross-sectional study	Ultrasonography	Abnormal albuminuria or eGFR ≤60 mL/min/1.73 m^2	343, 53%	138	NAFLD increased the risk of CKD (aOR: 1.93, 95% CI: 1.10–3.60, p=0.02) in patients with type 1 diabetes
Ahn *et al*., 2013[22]	Cross-sectional study	Ultrasonography	Proteinuria or eGFR ≤60 mL/min/1.73 m2	1,706, 32%	424	NAFLD increased the risk of CKD (aOR: 1.68, 95% CI: 1.27–2.24, p=0.02)
Wilechansky *et al*., 2019[27]	Community-based prospective cohort study	MDCT	eGFR <60 mL/min/1.73 m^2	987, 19%	19	Liver fat was not associated with the prevalence and incidence of CKD
Zhang *et al*., 2020[28]	Cross-sectional study	Ultrasonography	eGFR <60 mL/min/1.73 m^2 or and/or abnormal albuminuria and/or overt proteinuria	60,965, 29.8%	7,229	NAFLD was associated with an increased risk of early stages of CKD in both Chinese and USA cohort, but not the late stages of CKD
Sinn DH *et al*., 2017[29]	Retrospective cohort study	Ultrasonography, NAFLD severity assessed by APRI, NFS and FIB-4 score	eGFR <60 mL/min/1.73 m^2	41,430, 34.3%	691	NAFLD increased the risk of CKD (aHR: 1.22, 95% CI: 1.04–1.43, p=0.018), the degree of the risk was correlated with the severity of NAFLD
Park *et al*., 2019[30]	Retrospective propensity-matched cohort study	–	–	1,032,497, 25.4%	14,421	Compared with patients without NAFLD, patients with NAFLD had a 41% increased risk of developing advanced CKD (aHR: 1.41, 95% CI: 1.36–1.46, p=0.018), patients with decompensated cirrhosis had higher risk (aHR: 2.28, 95% CI: 2.12–2.46).
Chen *et al*., 2020[32]	Cross-sectional study	Ultrasonography, advanced liver fibrosis assessed by NFS	eGFR <60 mL/min/1.73 m^2	29,797, 44.5%	6,027	NAFLD was not related to CKD (OR=1.015, 95% CI: 0.954–1.081, p=0.630), but patients with advanced fibrosis tended to be more likely to have CKD (OR: 2.284, 95% CI: 1.513–3.448, p<0.001)

(continued)

Table 2. *(continued)*

Author, year	Study design	Diagnostic method for NAFLD	Diagnostic method for CKD	Sample size and rate of NAFLD	CKD incidence, *n*	Main findings
Zeng *et al*., 2017[23]	Cross-sectional study	Ultrasonography, CAP, FLI	eGFR <60 mL/min/1.73 m^2	731, 36.1%	48	NAFLD increased the risk of CKD regardless the diagnosis tools, when FLI ≥60 or CAP >292 dBm, eGFR was significantly reduced
Choudhary *et al*., 2016[24]	Retrospective cohort study	Histology	eGFR <60 mL/min/1.73 m^2	373, 50.1%	–	NAFLD did not affect renal function
Jang *et al*., 2018[33]	Cohort study	Ultrasonography	eGFR <60 mL/min/1.73 m^2	1,525, 40.9%	1,525	NAFLD was associated with the progression of CKD; the decrease of eGFR was greater in NAFLD patients than those who without (−0.79 vs. 0.30% per year, p=0.002)
Targher *et al*., 2010[21]	Cross-sectional study	Histology	eGFR ≤60 mL/min/1.73 m^2 and/or abnormal albuminuria	160, 50%	23	NAFLD increased the risk of CKD (aOR: 6.14, 95% CI: 1.6–12.8, p<0.001), the degree of the risk was correlated with the histologic severity of NASH
Kasim *et al*., 2020[35]	Cross-sectional study	Ultrasonography, abdominal CT scan or liver biopsy	eGFR <60 mL/min/1.73 m^2 and/or albuminuria	134, 50%	96	NAFLD had higher prevalence of CKD (40.3 vs. 16.4%, p=0.002) and more grade 3 among CKD patients (37.3% vs. 9%, p=0.001) than non-NAFLD
Arase *et al*., 2011[36]	Retrospective cohort study	Ultrasonography and liver enzymes	eGFR <60 mL/min/1.73 m^2 and/or overt proteinuria	5,561, 100%	263	Diabetes (HR: 1.92, 95% CI: 1.45–2.54, p<0.001), hypertension (HR: 1.69, 95% CI: 1.25–2.29, p<0.001), age of 50 years (HR: 2.67, 95% CI: 2.06–3.46, p<0.001), elevated serum GGT of 109 IU/L (HR: 1.35, 95% CI: 1.02–1.78, p=0.038), and eGFR of 60–75 mL/min/1.73 m^2 (HR: 2.75, 95% CI: 1.93–3.94, p<0.001) were risk factors of CKD among NAFLD
Luo *et al*., 2019[37]	Cross-sectional study	Ultrasonography	eGFR <60 mL/min/1.73 m^2 and/or albuminuria	515, 100%	282	Obesity was a risk factor for CKD among NAFLD patients (p<0.01)
Wijarnpreecha *et al*., 2018[38]	Cross-sectional study	Ultrasonography	eGFR <60 mL/min/1.73 m^2	4,142, 100%	200	Advanced liver fibrosis assessed by NFS (aOR: 4.92, 95% CI: 2.96–8.15) and FIB-4 (aOR: 2.27, 95% CI: 1.05–4.52) was associated with the risk of CKD
Sesti *et al*., 2014[39]	Cross-sectional study	Ultrasonography	eGFR <60 mL/min/1.73 m^2	570, 100%	38	Advanced liver fibrosis was independently associated with the risk of CKD
Yasui *et al*., 2011[40]	Cross-sectional study	Histology	eGFR <60 mL/min/1.73 m^2 or overt proteinuria	174, 100%	24	When contrasted to non-NASH NAFLD, the presence of NASH increased the incidence of CKD (21 vs. 6%, p=0.007)
Huh *et al*., 2017[41]	Population-based prospective cohort study	FLI	eGFR <60 mL/min/1.73 m^2	4,761, 12.62%	724	FLI ≥60 was associated with increased risk of CKD (HR: 1.459, 95% CI: 1.189–1.791, p=0.0012)
Chang *et al*., 2008[42]	Community-based cohort study	Ultrasonography	eGFR <60 mL/min/1.73L m^2 or the presence of proteinuria	8,329, 30%	324	NAFLD with elevated GGT increased the risk of CKD (a RR: 2.31, 95% CI: 1.53–3.50, p=0.008)
Tsai *et al*., 2020[43]	Cross-sectional study	Ultrasonography or FibroScan	eGFR <60 mL/min/1.73 m^2 or urine protein >2+	90, 100%	39	Some nontraditional indicators, such as VCAM-1, urinary level of FABP4 and RBP4, were shown to be predictors of CKD progression

aOR, adjusted odds ratio; APRI, aspartate aminotransferase to platelet ratio index; CT, computed tomography; FABP4, fatty acid-binding protein 4; GGT, γ-glutamyltransferase; MDCT, multidetector computed tomography; NFS, NAFLD fibrosis score; RBP4, retinol binding protein 4; VCAM-1, vascular cell adhesion molecule-1.

aHR=1.47, 95% CI: 1.36–1.59; decompensated cirrhosis: aHR=2.28, 95% CI: 2.12–2.46).[30] A meta-analysis involving 96,595 patients also revealed that the more severe NAFLD was in patients, the higher was the CKD risk (hazard ratio [HR]=1.50, 95% CI: 1.25–1.74), and this risk was even greater in NAFLD patients with high-median fibrosis scores (HR=1.59, 95% CI: 1.31–1.93).[31] However, Chen *et al*.[32] found that NAFLD itself does not affect CKD occurrence, but the presence of advanced liver fibrosis increases the risk of CKD. Therefore, CKD screening should be performed in NAFLD patients with advanced fibrosis.

In addition, increased hepatic lipid content in NAFLD patients was also reported to affect the incidence of CKD. Fatty liver index (FLI) and controlled attenuation parameter are some of the noninvasive indicators for diagnosis of hepatic steatosis; when FLI was ≥60 or controlled attenuation parameter was >292 dBm, the eGFR was observed to be significantly reduced.[23]

Since NAFLD was recently renamed to MAFLD, their definitions are slightly different, which may have some influence on CKD recognition. A recent study of 12,571 individuals confirmed that the diagnosis of MAFLD was more accurate than that of NAFLD with respect to CKD identification. MAFLD patients showed a higher prevalence of CKD than NAFLD patients, and the severity of MAFLD was associated with a 1.34-fold increased risk of CKD.[44]

The majority of current studies have thus supported the conclusion that NAFLD increases the risk of CKD, and the magnitude of the risk related to CKD occurrence is associated with NAFLD severity. Components of metabolic syndrome, such as DM and hypertension, also seem to play a role in this relationship. Therefore, controlling the progression of NAFLD and other metabolic diseases may benefit the kidneys.

Effects of NAFLD on CKD severity

A growing body of research has shown that NAFLD increases the risk of CKD and is also correlated with its severity. Jang *et al*.[33] found that among CKD patients, the decrease in eGFR was greater in NAFLD patients than in those without (−0.79% vs. 0.30% per year, p=0.002). The extent of decrease was greater in patients with higher fibrosis scores, suggesting that NAFLD severity has an impact on CKD progression.

Targher *et al*.[21] compared the results of 80 biopsy-proven NASH patients with those of control subjects and concluded that CKD incidence was significantly higher in the NASH patients. This relationship was not affected by the components of metabolic syndrome, with eGFR levels decreasing along with the increasing histological severity (fibrosis stage). A meta-analysis of 33 studies also showed that the presence of steatohepatitis (odds ratio [OR]=2.53, 95% CI: 1.58–4.05) and advanced fibrosis (OR=5.20, 95% CI: 3.14–8.61) increased the risk of CKD, and a positive correlation was also found between NAFLD severity and CKD stages.[34]

Ramadhan *et al*.[58] found that the presence of liver fibrosis increased the CKD risk by approximately 3.8 times in patients with NAFLD (95% CI: 1.07–13.79, p=0.035); meanwhile, the frequency of grades 2 and 3 CKD was higher in patients with liver fibrosis than in those without (p=0.034). Kasim *et al*.[35] also found more grade 3 CKD patients in the NAFLD group than in the control group (37.3% vs. 9.0%).

Existing studies have shown that NAFLD itself can increase the incidence of high-grade CKD, where CKD severity is also affected by the severity of steatosis and fibrosis. Therefore, we suggest that renal function in NAFLD patients should be carefully monitored to aid in the early identification of CKD, after which relevant steps could be taken to intervene in disease progression.

Risk factors for CKD in patients with NAFLD

To stabilize the condition of NAFLD patients, delay the disease progression, and improve the quality of patient life, the search for CKD predictors is crucial. The components of metabolic syndrome are often considered first. DM is a common comorbidity of NAFLD that contributes to adverse liver outcomes through a synergistic effect.[59] Studies have shown that about one-third of NAFLD patients have impaired renal functions, which is closely related to the presence of DM in patients.[36,60] While obesity and NAFLD are considered as risk factors for each other, the former is also reported as a risk factor for CKD.[37,61] Chon *et al*.[62] followed up with 1,774 patients with NAFLD and confirmed that significant weight loss reduced the risk of rapid decline in renal function and presence of CKD when compared with those with minimal weight changes (HR=0.598, 95% CI: 0.458–0.782; HR=0.531, 95% CI: 0.409–0.690, respectively). Thus, weight loss can be used as one of the measures to improve long-term kidney prognosis of patients with NAFLD.

The severity of NAFLD in patients also influences CKD occurrence. High noninvasive liver fibrosis scores, such as FIB-4 and NAFLD fibrosis scores, which reflect the degree of liver fibrosis in patients with NAFLD, were associated with an increased risk of CKD.[63] Both could be used clinically to exclude CKD in patients with NAFLD, and FIB-4 was found to be the most accurate one.[38,39] NASH is a phase in the progression of NAFLD, which is believed to be a driving factor for the development of liver fibrosis.[64,65] In contrast to non-NASH NAFLD, the presence of NASH increases the incidence of CKD (21% vs. 6%, p=0.007).[40] Moreover, the predictive power of the traditional CKD prediction model significantly improves when the FLI is added, which is a predictor of the degree of hepatic steatosis. The area under receiver operating characteristic curve was observed to increase from 0.816 to 0.818 (p=0.0615).[41,66] Studies have also shown that γ-glutamyl transferase concentration is not only associated with NAFLD severity but could also explain the risk of CKD in nondiabetic, nonhypertensive men, in spite of the metabolic syndrome.[42,67]

Recently, the ability of some nontraditional indicators to predict the incidence of CKD has also been investigated. Urinary neutrophil gelatinase-associated lipocalin, which is an early marker of renal tubular injury, was found to be a significant predictor for CKD in NAFLD patients who were diagnosed by biopsy or transient elastography, in a cross-sectional study. The cut-off value was reported to be 36.75 ng/mL, with the specificity of 85% and sensitivity of 75%; a higher incidence of CKD in advanced fibrosis has also been found (15.4 vs. 3.4%, p=0.056).[68,69] Fatty acid-binding protein plays an important role in liver lipometabolism and is associated with inflammation and fibrosis in NAFLD patients.[70] Retinol-binding protein 4 was also found to be significantly increased in patients with severe NAFLD.[71] Vascular cell adhesion molecule-1 is produced by liver cells through the stimulation of C-reactive protein, tumor necrosis factor-α, and other cytokines under the chronic inflammatory state, and is involved in the initiation of atherosclerosis; thus, it can be regarded as having a role in NAFLD pathogenesis.[72,73] All three indicators are considered proven as predictors of CKD progression in NAFLD patients with hypertension.[43]

In addition to the aforementioned risk factors that affect both NAFLD and CKD, there are some independent risk factors for each. In addition to the components of the metabolic syndrome, some genetic factors are believed to be related to the occurrence of NAFLD. The PNPLA3-I148M

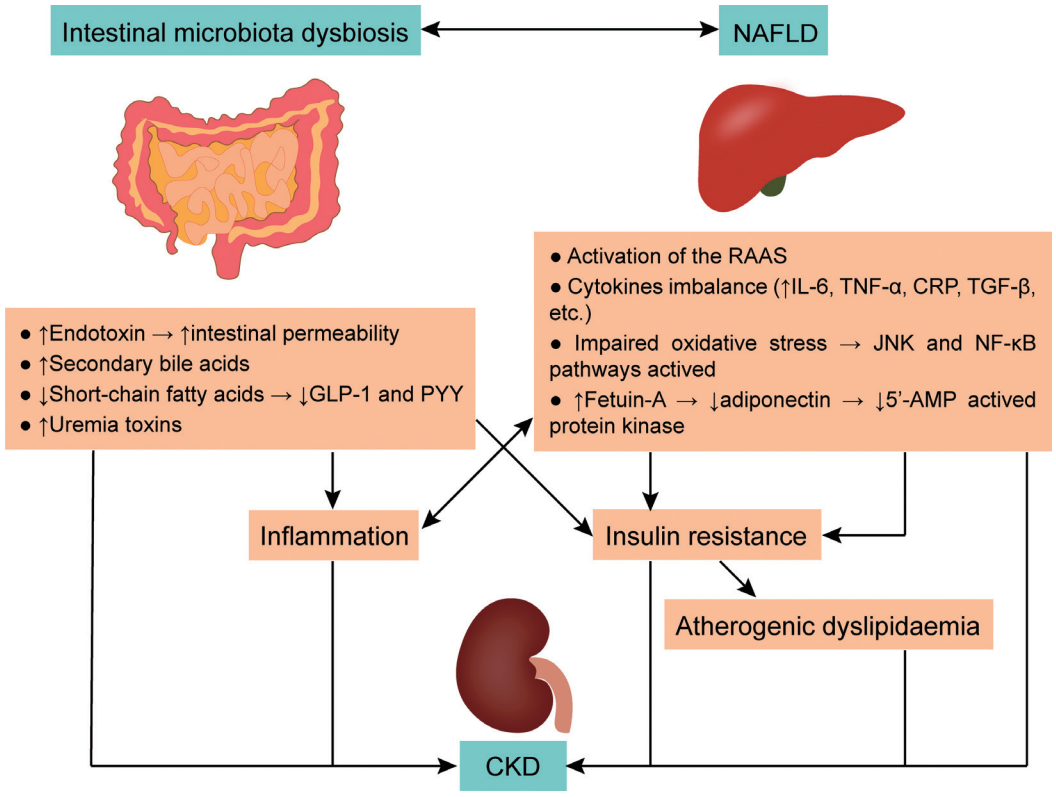

Fig. 1. Putative biological mechanisms linking NAFLD and CKD. In NAFLD patients, cytokine imbalance caused by increased release of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), transforming growth factor-β (TGF-β) and other cytokines lead to inflammation, then cause renal injury. Impaired oxidative stress activates the C-Jun-N-terminal kinase (JNK) and nuclear factor-κB (NF-κB) pathways, promoting systemic inflammatory response, further exaggerating oxidative stress. Renin-angiotensin-aldosterone system (RAAS) components produced by fat cells can promote the production of proinflammatory factors. Increased production of fetuin-A leads to downregulation of adiponectin levels, while the latter can reduce the activation of 5'-AMP-activated protein kinase, thereby exacerbating renal damage and insulin resistance. Insulin resistance can not only damage the kidneys directly but also indirectly by promoting the formation of atherogenic dyslipidemia. Under the state of intestinal microbiota dysbiosis, increased release of endotoxin destroys the intestinal barrier, then exaggerates inflammation. The increased production of uremia toxins excreted through urine is toxic to the kidneys. The increased production of secondary bile acids also produces proinflammatory effects. Meanwhile, the decreased production of short-chain fatty acids reduces the production of glucagon-like peptide-1 (GLP-1) and incretins peptide YY (PYY), which then aggravates insulin resistance. ↑ indicates an increase, ↓ indicates a decrease, and → signifies the consequences that result. CKD, chronic kidney disease; NAFLD, non-alcoholic fatty liver disease.

variant was found to be associated with the maximized risk of NAFLD when accompanied with adiposity.[74,75] HSD17B13 silencing was observed to reduce liver damage in patients with fatty liver.[76] In addition, a high-fat, high-sodium, low-nutrition diet, and low physical activity lifestyle are considered as risk factors for NAFLD.[77–79] Moreover, along with DM and hypertension, CKD could be caused by the use of nephrotoxic drugs as well as glomerular, infectious, and other diseases.[80,81] Sex and age also affect the incidence of CKD. CKD was most common in females and people of age >65 years,[82] indicating that elderly women should focus on the early detection of renal function abnormality.

In general, indicators of NAFLD severity, components of the metabolic syndrome, and some indicators related to renal function predict the risk of CKD in patients with NAFLD. Moreover, the risk factors individually related to the occurrence of NAFLD and CKD should not be ignored. A comprehensive evaluation of these factors has a certain guiding significance for clinical practice.

Putative biological mechanisms

With the ongoing studies on NAFLD and CKD, several metabolic comorbidities associated with NAFLD have been found to be potential risk factors for CKD. Because of the significant social, economic, and psychological burdens of the two diseases, the pathogenesis that links them needs to be identified. On the one hand, it can provide a new direction for treatment, on the other hand, the prevention of CKD occurrence in NAFLD patients would be possible. However, this pathogenesis is not clear at present. All the potential mechanisms are presented in Figure 1.

Inflammatory cytokines

The imbalance of cytokines may contribute to the development of CKD, the increased systematic release of various proinflammatory, procoagulant, profibrogenic, and pro-oxidant factors, such as tumor necrosis factor-α, transforming growth factor-β, C-reactive protein, interleukin-6, plasminogen activator inhibitor-1, and connective tissue growth factor (produced by hepatic stellate cells and Kupffer cells from the steatosis liver), may play significant roles in CKD occurrence.[83–85]

Oxidative stress

Impaired oxidative stress is also a potential pathogenic mechanism. Energy metabolism is reported to be accelerated and oxidative stress is observed to be increased by fat deposition in liver cells. Subsequently, C-Jun-N-terminal kinase and nuclear factor-κB pathways are activated, leading to an increase in the transcription of proinflammatory genes. This then promotes the systemic inflammatory response, exaggerates oxidative stress, enhances immunologic inflammatory responses of the kidney, and eventually leads to renal injury.[86–89]

Activation of the RAAS

Activation of the RAAS is also reported to be involved in the deterioration of renal function in NAFLD patients. Fat cells produce all RAAS ingredients and contribute as much as 30% of circulating angiotensin II, which promotes the production of proinflammatory factors and lipogenesis.[90] On the one hand, it can induce NAFLD progression, on the other hand can cause contraction of glomerular efferent arteriole through ectopic lipid deposition, thereby leading to inflammation and oxidative stress, followed by eventual development of glomerular sclerosis.[91]

Insulin resistance

The fact that NAFLD patients have increased visceral fat deposition and insulin resistance activated by C-Jun-N-terminal kinase-1 from adipose tissue has been confirmed in animal experiments.[92] Fetuin-A, produced by expanded and inflamed adipose tissue, has been found to play an important role in promoting insulin resistance.[93] However, renal hemodynamics are reported to deteriorate under the combined action, induced by insulin resistance, activation of the sympathetic nervous system, downregulation of the natriuretic peptide system, and generation of sodium retention, ultimately promoting renal disease progression.[84,94] Adiponectin is a protein that has anti-inflammatory and antiatherogenic capacities and is secreted by adipose tissue.[95] In patients with NAFLD, high fetuin-A levels are often reported to cause downregulation of adiponectin levels. Hypoadiponectinemia is observed to mediate damage to hepatocytes and renal podocytes by reducing the activation of 5′AMP-activated protein kinase, thereby promoting renal inflammation and fibrosis and exacerbating insulin resistance.[83,96].

Atherogenic dyslipidemia

The formation of atherogenic dyslipidemia can be promoted by insulin resistance, which is characterized by high levels of triglycerides and small, dense low-density lipoprotein cholesterol, and low levels of high-density lipoprotein cholesterol. This is then associated with renovascular damage, renal endothelial dysfunction, and glomerular injury.[95,97,98]

Intestinal microbiota dysbiosis

Intestinal microbiota dysbiosis is common in patients with NAFLD. Increased release of endotoxin from Gram-negative bacteria destroys the intestinal barrier, thus increasing intestinal permeability. The introduction of endotoxin into the blood increases circulating lipopolysaccharide levels, thus leading to the systemic inflammatory state and thereby increasing CKD risk.[99] Indole produced by *Escherichia coli,* and p-cresol and trimethylamine produced by many obligate or facultative anaerobes, such as genera *Bacteroides, Enterobacter,* and *Clostridium diffificile*,[100,101] are further metabolized by the liver to produce trimethylamine-N-oxide, p-cresol sulfate and indole sulfate, which are excreted through urine but toxic to the kidneys.[102] The phenomenon whereby trimethylamine-N-oxide induces atherosclerosis[103] and leads to renal fibrosis has been demonstrated.[104] Increased production of secondary bile acid dysregulates the farnesoid X nuclear receptor system, which can improve liver histology in NASH by being activated[105] and induces DNA damage in hepatic stellate cells through enterohepatic circulation, thereby increasing the secretion of various tumor-promoting and inflammatory factors. Thus, a systemic inflammatory state is formed and risk of CKD increases.[106] Decrease in short-chain fatty acids produced by *Lactobacilli* and *Bifidobacteria* in NAFLD patients can reduce the production of glucagon-like peptide-1 and incretins peptide YY, which are produced after the activation of the short-chain fatty acids receptor, and is believed to increase insulin secretion and improve satiety. Thereby, the reduction of these two substances can aggravate insulin resistance, leading to kidney damage.[107,108]

The pathogenesis linking NAFLD and CKD has not been confirmed yet, but inflammation, oxidative stress, activation of the RAAS, insulin resistance, intestinal microbiota dysbiosis, as well as a series of downstream effects caused by them seem to all play a role in the pathogenesis of both diseases. However, further studies are warranted to explain the contribution of each of the factors to the incidence of CKD.

Perspectives

Although there is increasing evidence demonstrating an association between NAFLD and CKD, further improvement of experimental design is required to fulfil the limitations of the existing studies. First, most studies are cross-sectional studies that could not establish an exact causality between the two diseases. On the other hand, the efficiency of the retrospective study design is insufficient; therefore, multicenter prospective studies are required. Second, conducting liver biopsy routinely is not realistic and fat deposition in NAFLD patients is also considered to be patchy, which further increases the chance of misdiagnosis. Thus, most studies have diagnosed NAFLD through ultrasound; however, a biopsy is expected to be included in future experiments as a diagnostic gold standard. Third, due to different adjustments for confounding factors, the strength of the correlation between the two diseases obtained from different studies has a discrepancy; the usage of drugs, such as antihypertensive drugs and cholesterol-lowering agents, and drugs effecting renal functions, were often not included in the studies. Therefore, it is necessary to further complete the clinical data of the patients. Fourth, CKD has many pathologies and their prognoses vary massively. No study has investigated the relationship between NAFLD and the different pathological types of CKD, which needs to be further explored. Fifth, the pathogenesis linking NAFLD and CKD is still not specific, and the contribution of various potential mechanisms causing renal insufficiency in NAFLD patients is also unclear. To conduct accurate treatment and target the etiology, further experiments need to be conducted.

Conclusions

Recent studies have suggested that NAFLD is associated with an increased risk of CKD, but more proof is needed for confirmation. Inflammatory cytokines, oxidative stress,

activation of RAAS, insulin resistance, atherogenic dyslipidemia, and intestinal microbiota dysbiosis were reported as potential pathogenesis. Early detection of CKD in NAFLD patients by monitoring the renal function closely to reduce the incidences of liver and kidney transplants is expected to attract the attention of clinicians. On the other hand, CKD patients are also suggested to closely examine their hepatic fatty deposition levels. Numerous studies are hence needed to suggest a proper treatment in the future.

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Conflict of interest

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Author contributions

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