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Contents

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## EVIDENCE REVIEW



## REVIEW



## MINIREVIEWS



## ORIGINAL ARTICLE

### Basic Study

## Retrospective Study



## Observational Study

## ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Abhinav Vasudevan, Bachelor of Medicine, MPH, PhD, FRACP, Advanced Inflammatory Bowel Disease Fellow, Mayo Clinic, 200 1st Street SW, Rochester, MN 55902, United States. vasudevan.abhinav@mayo.edu

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*REVIEW*

# Non-alcoholic fatty liver and chronic kidney disease: Retrospect, introspect, and prospect

Rajiv Heda, Masahiko Yazawa, Michelle Shi, Madhu Bhaskaran, Fuad Zain Aloor, Paul J Thuluvath, Sanjaya K Satapathy

**ORCID number:** Rajiv Heda 0000-002-5556-5784; Masahiko Yazawa 0000-0002-3907-5347; Michelle Shi 0000-0002-1387-3770; Madhu Bhaskaran 0000-0002-8903-9301; Fuad Zain Aloor 0000-0002-2508-4517; Paul J Thuluvath 0000-0002-4374-4507; Sanjaya K Satapathy 0000-0003-0153-2829.

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**Rajiv Heda,** Department of Internal Medicine, Tulane University School of Medicine, New Orleans, LA 70112, United States

**Masahiko Yazawa,** Department of Nephrology and Hypertension, St. Marianna University School of Medicine, Kawasaki 216-8511, Japan

**Michelle Shi, Sanjaya K Satapathy,** Department of Internal Medicine, Donald and Barbara Zucker School of Medicine, Northwell Health, Manhasset, NY 11030, United States

**Madhu Bhaskaran,** Department of Nephrology, Northwell Health/Zucker School of Medicine at Hosftra, Manhasset, NY 11030, United States

**Fuad Zain Aloor,** Department of Internal Medicine, Baylor College of Medicine, Houston, TX 77030, United States

**Paul J Thuluvath,** Institute of Digestive Health & Liver Diseases, Mercy Medical Center, Baltimore, MD 21202, United States

**Corresponding author:** Sanjaya K Satapathy, FAASLD, AGAF, FACG, MBBS, MD, Professor, Department of Internal Medicine, Donald and Barbara Zucker School of Medicine, Northwell Health, 400 Community Drive, Manhasset, NY 11030, United States. ssatapat@northwell.edu

## Abstract

With the growing prevalence of obesity and diabetes in the United States and across the world, a rise in the overall incidence and prevalence of non-alcoholic fatty liver disease (NAFLD) is expected. The risk factors for NAFLD are also associated with the development of chronic kidney disease (CKD). We review the epidemiology, risk factors, genetics, implications of gut dysbiosis, and specific pathogenic mechanisms linking NAFLD to CKD. Mechanisms such as ectopic lipid accumulation, cellular signaling abnormalities, and the interplay between fructose consumption and uric acid accumulation have led to the emergence of potential therapeutic implications for this patient population. Transplant evaluation in the setting of both NAFLD and CKD is also reviewed. Potential strategies for surveillance and management include the monitoring of comorbidities, the use of non-invasive fibrosis scoring systems, and the measurement of laboratory markers. Lastly, we discuss the management of patients with NAFLD and CKD, from preventative measures to experimental interventions.

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**Core Tip:** Patients with non-alcoholic fatty liver disease (NAFLD) are at higher risk for the development of chronic kidney disease (CKD) than the general population. The prevalence of mutual comorbidities in addition to direct pathogenic mechanisms linking NAFLD to the development of CKD can explain this finding. With the breadth of data linking NAFLD to CKD, there are minimal options for treating this patient population. Regardless, we have presented strategies that can be implemented at various levels including surveillance, preventative, and management level.

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## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of chronic liver disease ranging from steatosis on one end to fibrosis and cirrhosis on the other end[1]. NAFLD and non-alcoholic steatohepatitis (NASH) are the hepatic manifestations of metabolic syndrome (MetS), which is a driving force for a multitude of comorbidities, such as insulin resistance, cardiovascular disease (CVD), chronic kidney disease (CKD), obstructive sleep apnea (OSA), as well as increased malignancy risk[2]. While NASH is the second leading indication for liver transplantation (LT), it is expected that NASH will overtake hepatitis C virus (HCV) as the leading cause, given the efficacy of direct-acting antiviral therapy[3]. A recent epidemiological study has already confirmed a downward trend for HCV-related LT in the United States[4].

NAFLD is tightly linked to underlying insulin resistance and is associated with other comorbidities related to MetS[5]. Growing evidence suggests that NAFLD is a risk factor for CKD[6] due to shared metabolic risk factors[7]. Of note, several studies have shown an association between the severity of NASH and CKD[8-11]. Interestingly, a meta-analysis of 33 studies showed that diabetes status and metabolic risk factors had no impact on the positive correlation between the severity of NASH and CKD[12], suggesting a possible unique pathogenic link between NAFLD and CKD irrespective of their shared metabolic risk factors. We review the genetic, epidemiologic, and pathogenic links between NAFLD and CKD in addition to potential preventative and management strategies.

## PREVALENCE OF CKD IN NAFLD AND POTENTIAL PREDISPOSING RISK FACTORS

Two meta-analyses and a retrospective cohort analysis suggest that the incidence and prevalence of CKD increase in patients with NAFLD compared to patients without NAFLD (Table 1). In all analyses, the magnitude and direction of effects remained unaffected by diabetes status, even after adjustment for other risk factors[12-14]. Moreover, the association was stronger in patients with advanced fibrosis or decompensated cirrhosis as compared to compensated cirrhosis. The studies that were included in these major meta-analyses defined advanced fibrosis was defined by histological parameters, imaging findings, and/or elevations in the NAFLD fibrosis score (NFS). Of note, among 42 studies included in these two meta-analyses, only 13 ($n$ = 2205) utilized liver histology, which is the gold standard in diagnosing NAFLD[15]. The majority of the studies established diagnosis of NAFLD *via* abdominal ultrasound, liver enzyme elevation [including serum gamma-glutamyl transferase (GGT)

**Table 1 Incidence and prevalence of chronic kidney disease in patients with varying degrees of non-alcoholic fatty liver disease severity**

| Ref. | Year | *n* | NAFLD diagnostic modalities | Conclusion(s) |
|---|---|---|---|---|
| Musso *et al*[12]. A meta-analysis of 33 studies | 2014 | 63902 | Liver biopsy, abdominal ultrasound, elevated liver enzymes | (1) 20 cross-sectional studies: Nearly two-fold increased risk of CKD in patients with NAFLD (OR 2.12, 95%CI 1.69-2.66); (2) 11 longitudinal studies: 1.8-fold increased risk of CKD in patients with NAFLD (HR 1.79, 95%CI 1.65–1.95); and (3) advanced fibrosis associated with increased prevalence (OR 5.20, 95%CI 3.14-8.61) and incidence (HR 3.29, 95%CI 2.30-4.71) of CKD in patients with NAFLD |
| Mantovani *et al*[13]. A meta-analysis of 9 studies | 2018 | 96595 | Abdominal ultrasound; FLI; serum GGT | Incidence of CKD: (1) 1.4-fold increased long-term risk (HR 1.37, 95%CI 1.20–1.53) in patients with NAFLD with a median follow-up period of 5.2 years; and (2) 1.5-fold increased risk (HR 1.50, 95%CI 1.25-1.74) in patients with severe NAFLD (defined as NFS ≥ -1.455 or serum GGT ≥ 109 U/L) |
| Park *et al*[14]. Retrospective Cohort with Propensity Score Matching (1:3) | 2019 | 262619 | ICD-9 | Incidence of CKD: 1.4-fold increased risk (aHR 1.41; 95%CI, 1.36-1.46) in patients with NAFLD after adjusting for demographics, baseline covariates, and ACEi/ARB use; Risk of incident CKD increases as the severity of NAFLD increases: (1) compensated cirrhosis (aHR, 1.47; 95%CI 1.36-1.59); and (2) decompensated cirrhosis (aHR, 2.28; 95%CI 2.12-2.46) |

NAFLD: Non-alcoholic fatty liver disease; CKD: Chronic kidney disease; HR: Hazard ratio; FLI: Fatty liver index; GGT: Gamma glutamyl transferase; NFS: NAFLD fibrosis score; CI: Confidence interval; OR: Odds ratio; ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ICD-9: International classification of disease-9.

elevation], or using international classification of disease-9 code.

Previous review articles estimated that the prevalence of CKD was 20% to 55% in patients with NAFLD, whereas the prevalence of CKD in patients without NAFLD was 5% to 30%[16,17]. However, most of these reviews evaluated the same pool of data[8,9,11,18-22], which were also included in the two meta-analyses mentioned above. Our conclusions were based on studies that were published before 2015 as several more recent studies did not use histology or imaging for NAFLD diagnosis[23-26].

Many non-hepatic and hepatic risk factors are associated with CKD in those with NAFLD.

### Non-hepatic risk factors

There is minimal data on non-hepatic risk factors to predict which patients will go on to develop CKD. However, there are a few studies outlined below to identify which patients may be at higher risk (Table 2).

### Smoking

Current cigarette smoking is associated with CKD or death from end-stage renal disease. Mainstream cigarette smoke includes over 4000 compounds, and nicotine is one of many biologically stable and active compounds present in tobacco. Nicotine causes kidney damage by modulating α7nAChR, NLRP6 inflammasome, ER stress, and autophagy[27,28]. Studies examining the relationship between smoking and NAFLD are lacking; however, in a cohort study of 1525 CKD patients who underwent repeated health check-up examinations over 10 years, the decline in estimated glomerular filtration rate (eGFR) associated with NAFLD was greater in current smokers, hypertensive patients, or those with lower eGFR at baseline had greater age- and sex-adjusted decline in eGFR[29].

### Diabetes

Around one-third of patients with NAFLD have impaired renal function and its prevalence in patients with NAFLD is dependent on the severity of liver disease and presence of diabetes mellitus[30]. The development of NAFLD in patients with diabetes appears to be an important event in its natural history predisposing these patients to a higher risk for developing CKD. Type 2 diabetes mellitus (T2DM) increases the risk of serious NASH and advanced fibrosis in patients with NAFLD[31,32]. Patients with T2DM or type 1 diabetes mellitus and NAFLD are at an increased risk of developing CKD compared to diabetics without NAFLD[20,33,34]. Despite accumulating evidence for NAFLD as a driver for CKD, the shared common risk factors make it difficult to isolate diabetes as an independent risk factor for CKD in NAFLD patients.

**Table 2 Summary of studies assessing non-hepatic risk factors for chronic kidney disease in patients with non-alcoholic fatty liver disease**

| Ref. | Risk factor(s) | Year | *n* | Comparison | Findings |
|---|---|---|---|---|---|
| Önnerhag *et al*[147] | Older age | 2019 | 120 | Biopsy-proven NAFLD *vs* non-NAFLD | Higher prevalence of CKD in patients ≥ 55 years old |
| Targher *et al*[20] | Diabetes mellitus | 2008 | 2103 | NAFLD and T2DM *vs* T2DM only | Patients with NAFLD and T2DM independently associated with increased risk of CKD (OR 1.87; 95%CI 1.3-4.1, $P$ = 0.020) |
| Targher *et al*[33] | Diabetes mellitus | 2010 | 301 | NAFLD and T1DM *vs* T1DM only | Patients with NAFLD and T1DM independently associated with increased risk of CKD |
| Jang *et al*[29] | Elevated baseline eGFR, HTN, and current smoking | 2018 | 1525 | NAFLD *vs* Non-NAFLD | The decline in eGFR associated with NAFLD appeared to be stronger among patients who were current smokers, hypertensive, and lower eGFR at baseline |

NAFLD: Non-alcoholic fatty liver disease; CKD: Chronic kidney disease; T2DM: Type 2 diabetes mellitus; OR: Odds ratio; CI: Confidence interval; T1DM: Type 1 Diabetes Mellitus; eGFR: Estimated glomerular filtration rate; HTN: Hypertension.

### *Hypothyroid*

Proper thyroid function is implicated in renal blood flow, glomerular and tubular function, electrolyte homeostasis, hepatic lipid metabolism, and fatty acid beta-oxidation[35]. Hypothyroidism can cause NAFLD through fat accumulation, while hyperthyroid can cause NAFLD through reactive oxygen species formation[36]. Additionally, the prevalence of hypothyroidism increases for each 10 mL/min/1.73 $m^2$ decrement in eGFR[37], and patients with hypothyroidism were more than 2 times likely to have NAFLD and 4 times more likely to have NASH[38].

### *Hepatic risk factors*

**NAFLD-related advanced fibrosis:** Patients with NAFLD-related advanced fibrosis are more likely to have CKD compared to patients with NAFLD but without advanced fibrosis[39]. The risk of albuminuria increases with the severity of NAFLD-related advanced fibrosis, according to a 2017 study of 1763 Chinese diabetic patients[40]. After adjusting for common CKD risk factors such as diabetes and other metabolic comorbidities, advanced fibrosis but not steatosis was associated with a higher risk of albuminuria (OR: 1.52; 95%CI: 1.02-2.28; $P$ = 0.039). In a 2019 study of 594 patients with T2DM, significant liver fibrosis as detected by elastography (LSM ≥ 7.0/6.2 kPa) was independently associated with a higher risk of CKD (adjusted OR: 3.6, 95%CI: 1.3-10.1; $P$ = 0.01) in addition to CVD and other microvascular complications[41]. Increased liver stiffness as detected by transient elastography is a predictor of CKD in patients with ultrasound-diagnosed NAFLD[42]

In a 12-year prospective cohort, patients with non-obese NAFLD had a higher risk of developing CKD than patients with obese NAFLD[43]. A recent study has noted that the risk of developing CKD is higher in metabolically unhealthy non-obese NAFLD patients than their counterparts with metabolically healthy status defined by the lack of metabolic risk factors (*i.e.* diabetes mellitus, low High-density lipoprotein, hypertriglyceridemia, arterial hypertension)[44].

**Pathophysiology:** CKD secondary to fatty liver is thought to be due to systemic low-grade inflammation[45], which may involve upregulation of the nuclear factor-κB (NF-κB) pathway[45,46]. As discussed earlier, there is circumstantial evidence to suggest that patients with NASH-related advanced fibrosis have an increased prevalence of CKD. Progression of NASH may be partly mediated by the altered renin-angiotensin-aldosterone system due to CKD has also been proposed as a mechanism for NAFLD progression[47]. Although direct pathogenic links between NAFLD and CKD seem to be confounded by common metabolic comorbidities, novel mechanisms have been described.

**Insulin resistance**: Increased adiposity leads to increased free fatty acids and pro-inflammatory cytokine release that causes systemic insulin resistance (IR), which is an established mediator of NAFLD. IR is further exacerbated by the progression of NAFLD, leading to atherogenic dyslipidemia and further release of inflammatory cytokines resulting in CKD as shown in animal models[48]. Proinflammation occurs through the NF-κB and Jun-N-terminal kinase (JNK) pathways; activation of adipose-specific JNK pathways has been shown to cause insulin resistance[48,49]. As NAFLD

progresses to NASH, the inflammatory component is neutrophil-predominant and can cause systemic endothelial dysfunction (Figure 1)[50,51]. Notably, IR leads to increased production of very-low-density lipoprotein and endoplasmic reticulum stress, both of which can cause podocyte damage in glomeruli[52]. These latter two mechanisms have been linked to proteinuria and subsequent hastening of CKD[53,54].

**Ectopic lipid accumulation:** In animal models, a high fat/fructose diet resulted in increased urinary albumin excretion, elevated transaminases, and increased incidence of liver tumors when compared to a standard diet. Microscopically, lipid deposition leads to accelerated hepatorenal pathologies, suggesting that intracellular lipid accumulation may link NAFLD to CKD[55]. When treated with fenofibrate, slower intracellular lipid accumulation was noted in co-incidence with slower progression of renal and hepatic pathologies[55].

**Wnt signaling abnormalities:** Alterations in cellular pathways critical for homeostasis play an important role in the development of CKD in patients with NAFLD. Specifically, abnormalities in the Wnt (named as a fusion of the Drosophila gene wingless and its vertebrate homolog, integrated) signaling pathway have been linked to lipid accumulation, chronic inflammation, and fibrosis in the development of both NAFLD and CKD[56].

**Sterol regulatory element-binding proteins**: Sterol regulatory-element binding proteins are activated in a nutrient-rich (*i.e.*, anabolic) state that leads to insulin-signaling and increased endoplasmic reticulum stress, which can cause increased lipogenesis and hepatosteatosis. These changes cause the progression of other metabolic phenomena such as CKD and MetS[57].

**Fructose consumption and uric acid accumulation:** Fructose intake has been linked to hepatorenal injury *via* uric acid accumulation by altering the gut microbiome (Figure 2)[45,58]. Patients with a normal body mass index (BMI) and elevated serum uric acid levels (> 10 mg/dL) have an increased prevalence of MetS when compared to patients with a serum uric acid < 6 mg/dL[59], which is corroborated by other studies[60-62]. An increase in serum uric acid levels is also associated with an increase in the incidence of NAFLD[63]. In patients with NAFLD, elevated uric acid levels are known to be pathogenic in CKD progression[42,64]. These studies suggest that MetS, NAFLD, and CKD are interconnected through elevated serum uric acid levels[65].

Uric acid stimulates fructokinase, which sensitizes hepatocytes to fructose metabolism, subsequently leading to fat deposition in the liver, thereby explaining the link between elevated uric acid and NAFLD[66]. Elevated uric acid levels in animal models lead to glomerular hypertension and tubulointerstitial fibrosis, two processes that preclude the development of CKD[64]. Decreased urate clearance in CKD patients may further exacerbate this pathology. Interestingly, xanthine oxidase inhibitors are currently being tested in patients with CKD to monitor for disease progression in the CKD-FIX[67].

**Gut dysbiosis:** Changes in the gut microbiome play a role in the pathogenesis of NAFLD and CKD[45]. Dietary conditions such as increased fructose intake and vitamin D deficiency are shown to cause dysbiosis, which may directly lead to low-grade inflammation responsible for the development of NAFLD and CKD[45]. Dysbiosis and subsequent microbial fermentation lead to increased production of uremic toxins indoxyl sulfate and p-cresyl sulfate, which correlate directly with the progression of CKD[68]. The liver cytochrome P450 enzymes are directly regulated by these uremic toxins derived from alterations in gut microbial metabolism, hence the gut-liver-kidney axis[69]. Animal models have also shown the gut microbiota's ability to metabolize choline into trimethylamine N-oxide (TMAO), which is considered both nephrotoxic and hepatotoxic. In a 2015 study comparing TMAO levels in patients with CKD ($n$ = 521) to healthy patients ($n$ = 3166), median TMAO levels among CKD patients were significantly higher ($P$ < 0.001)[70]. Similarly, a 2019 case-control study comparing patients with NAFLD ($n$ = 34) to those without ($n$ = 14) showed that TMAO has a role in aggravating liver steatosis[71]. Lastly, certain species in the gut microbiota produce short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate and diffuse through gut mucosa, which can disrupt the integrity of the intestinal barrier. In the bloodstream, SCFAs can cause systemic inflammation, the common pathogenic link between NAFLD and CKD[45].

**Genetic links between NAFLD and CKD:** Two gene variants associated with both CKD and NAFLD are the G allele of the *patatin-like phospholipase domain-containing* (

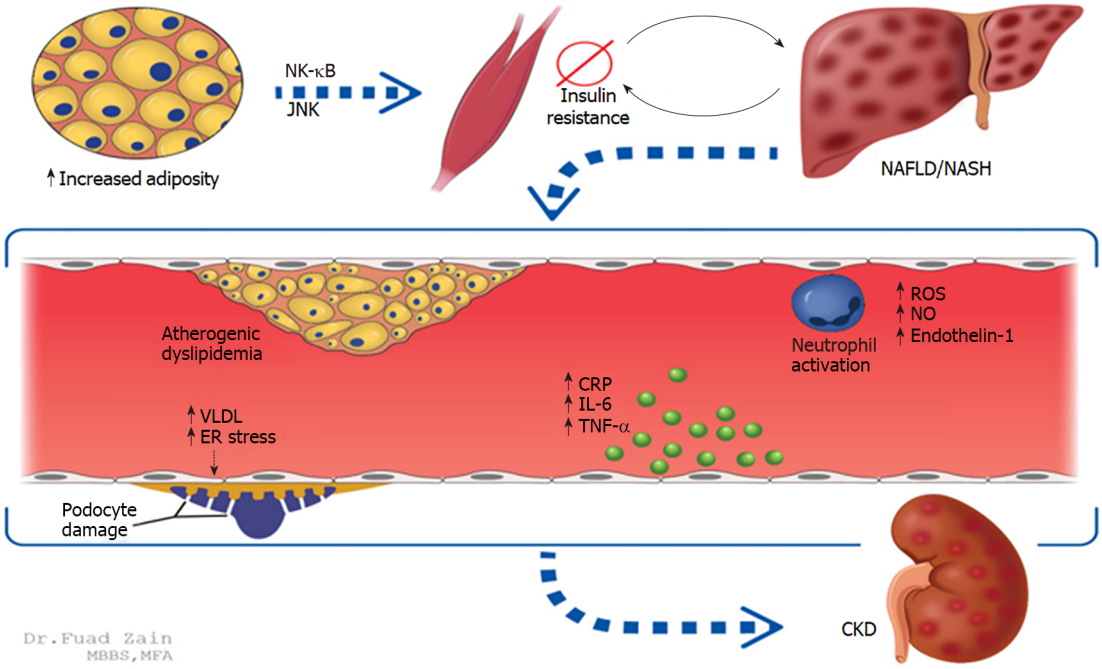


**Figure 1 Two established mechanisms between non-alcoholic fatty liver disease and the development of chronic kidney disease are increased adiposity and insulin resistance.** NF-κB: Nuclear factor-κB; JNK: Jun N-terminal kinases; NAFLD/NASH: Non-alcoholic fatty liver disease/Non-alcoholic steatohepatitis; ROS: Reactive oxygen species; NO: Nitric oxide; CRP: C-reactive protein; IL-6: Interleukin-6; VLDL: Very low-density lipoprotein; TNF-α: Tumor necrosis factor alpha; CKD: Chronic kidney disease

*PNPLA3)* gene and the T allele of the *transmembrane 6 superfamily member 2* (*TM6SF2*) gene. The G allele in the rs738409 polymorphism of the *PNPLA3* gene has been shown to play a major role in the progression of NASH[72,73]. Patients with the G allele also have been shown to have lower eGFR, increased incidence of microalbuminuria, and increased prevalence of CKD, regardless of NAFLD/NASH status[74,75]. The patient population that was found to have the highest risk of CKD and NAFLD in a 2015 study were patients who carried the G allele of the *PNPLA3*; furthermore, these patients were not obese, which is an important risk factor for CKD[75]. Another study showed that Chinese patients with normal alanine aminotransferase levels who carried the rs738409 polymorphism in the *PNPLA3* gene were at risk for early glomerular and tubular damage, which could explain why these patients develop CKD even in the absence of well-known risk factors, such as obesity or diabetes[76]. In postmenopausal women with T2DM, having the G/G allele leads to a higher prevalence of CKD, regardless of NAFLD status, further supporting the argument that this polymorphism may be an independent predictor for CKD[77]. Patients who are found to have the G/G allele in the polymorphism rs738409 should have close monitoring for the development of NAFLD as well as renal dysfunction, even in normal-weight patients[75]. On the other hand, the rs58542926 polymorphism on the *TM6SF2* gene, also known as the T allele of the *TMS6F2* gene, has been associated with the development of NAFLD[78] but has also been associated with a higher eGFR and lower prevalence of microalbuminuria[74]. Thus, this specific polymorphism in *TM6SF2* may be nephroprotective in patients with NAFLD.

### *Identifying NAFLD patients at risk for progression of CKD*

**Role of non-invasive fibrosis scoring systems:** Non-invasive scoring systems are utilized in assessing the severity of various chronic liver diseases. However, they have also been shown in several studies to be useful in predicting CKD in patients with NAFLD (Table 3). Incremental increases in the fatty liver index are an independent risk factor for developing CKD in a 10-year prospective analysis of 6238 adults (age 40-69 years) without CKD at baseline[23]. In another study of 11376 Taiwanese subjects, the NFS was negatively correlated with eGFR[6]. Multiple studies show that patients who have an intermediate and high-risk category of fibrosis-4 index (FIB-4)-index and NFS are at an increased risk of CKD[79,80], while a 2019 cross-sectional study of 11836

**Table 3 Summary of studies assessing non-invasive scoring systems for advanced fibrosis to assess risk for chronic kidney disease in patients with nonalcoholic fatty liver disease**

| Ref. | Year | *n* | Scoring system(s) assessed | Results |
|---|---|---|---|---|
| Ciardullo *et al*[82] | 2020 | 2770 | APRI, FIB-4, FLI, NFS | NAFLD-related fibrosis as measured with FIB-4 associated with CKD ($P < 0.01$) |
| Hsieh *et al*[6] | 2020 | 11376 | NFS | Higher NFS associated with impaired eGFR ($P < 0.0001$) |
| Choi *et al*[81] | 2019 | 11836 | APRI, BARD, FIB-4, FLI | FIB-4 ($P = 0.0258$) most precise in predicting kidney dysfunction |
| Önnerhag *et al*[79] | 2019 | 144 | APRI, BARD, NFS, FIB-4 | High-risk NFS ($P < 0.001$), FIB-4 ($P < 0.001$), APRI ($P = 0.008$) predict CKD |
| Wijarnpreecha *et al*[80] | 2018 | 4142 | APRI, BARD, NFS, FIB-4 | High/intermediate probability of liver fibrosis on NFS (AUC = 0.75) and FIB-4 (AUC = 0.77) independently predict CKD |
| Huh *et al*[23] | 2017 | 6238 | FLI | NAFLD cut-off for NAFLD is an independent RF for CKD ( $P < 0.0001$) |

NFS: Nonalcoholic fatty liver disease fibrosis score; FIB-4: Fibrosis-4 index; APRI: Aspartate aminotransferase to platelet ratio index; FLI: Fatty liver index; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; AUC: Area under the curve; RF: Risk factor; BARP: Biologically-oriented Alveolar Ridge Preservation; NAFLD: Nonalcoholic fatty liver disease.

patients showed that FIB-4 is the most precise tool when estimating renal dysfunction attributable to NAFLD (area under the curve = 0.6227, 95%CI: 0.5929-0.6526, $P = 0.0258$) after adjusting for various demographic and clinical variables[81]. FIB-4 is the most superior predictor in other studies as well[80,82]. In summary, patients with NAFLD-related fibrosis are at increased risk for CKD, and these patients should undergo proper surveillance *via* non-invasive fibrosis scoring systems and/or advanced imaging techniques (*i.e.* Fibroscan, TE) (Figure 3).

**Cystatin C:** Serum creatinine, a widely used biomarker in assessing renal function, is inaccurate in determining GFR in patients with cirrhosis[83]. This is due to muscle wasting that occurs in cirrhosis, thus leading to diminished creatinine formation, increased tubular secretion of creatinine, and impaired assay interpretation caused by elevated bilirubin[83]. Alternatively, the measurement of cystatin C does not have the same limitations as serum creatinine due to its low molecular weight and because it does not require adjustment for gender, mass, or bilirubin level[84]. A combination of serum creatinine and cystatin C is more accurate in determining GFR than serum creatinine alone[85]. However, serum creatinine alone is superior for patients without cirrhosis[85]. Measurement of cystatin C in addition to serum creatinine may have utility for accurately assessing renal function in transplant candidates and for monitoring the development of CKD in patients with NASH cirrhosis. Although the cost of measuring eGFR using Cystatin C in addition to serum creatinine is higher, the burden of over-diagnosing CKD in patients with cirrhosis is lessened, which may lead to an overall reduction in unnecessary medical expenses for patients with cirrhosis who truly have CKD[86].

**Alkaline phosphatase and GGT:** In diabetic patients with NAFLD, serum alkaline phosphatase (ALP), a NAFLD-associated marker when elevate, was also significantly associated with impaired renal function[87,88]. Interestingly, ALP is associated with the release of proinflammatory cytokines from the liver that are known to disrupt the glomerular endothelial glycocalyx, leading to albuminuria, which may explain why ALP is a potential surveillance marker in patients with NAFLD who are at risk for developing CKD[89]. Furthermore, elevated serum GGT is associated with an increased risk of CKD[24,90,91]. GGT is associated with increased inflammatory markers and insulin resistance, both of which play central roles in patients with NAFLD who develop CKD[24,92]. However, elevated GGT may not be an accurate CKD parameter in Caucasian men, as GGT is confounded by BMI, lifestyle factors, and lipids, as noted in a 2017 study[25]. Therefore, elevated GGT in Caucasian men with NAFLD should be interpreted with caution when monitoring for CKD. Of importance, NAFLD was diagnosed by elevated GGT levels (in addition to ultrasound in only one study[91]; therefore, these findings may not apply to patients diagnosed by more

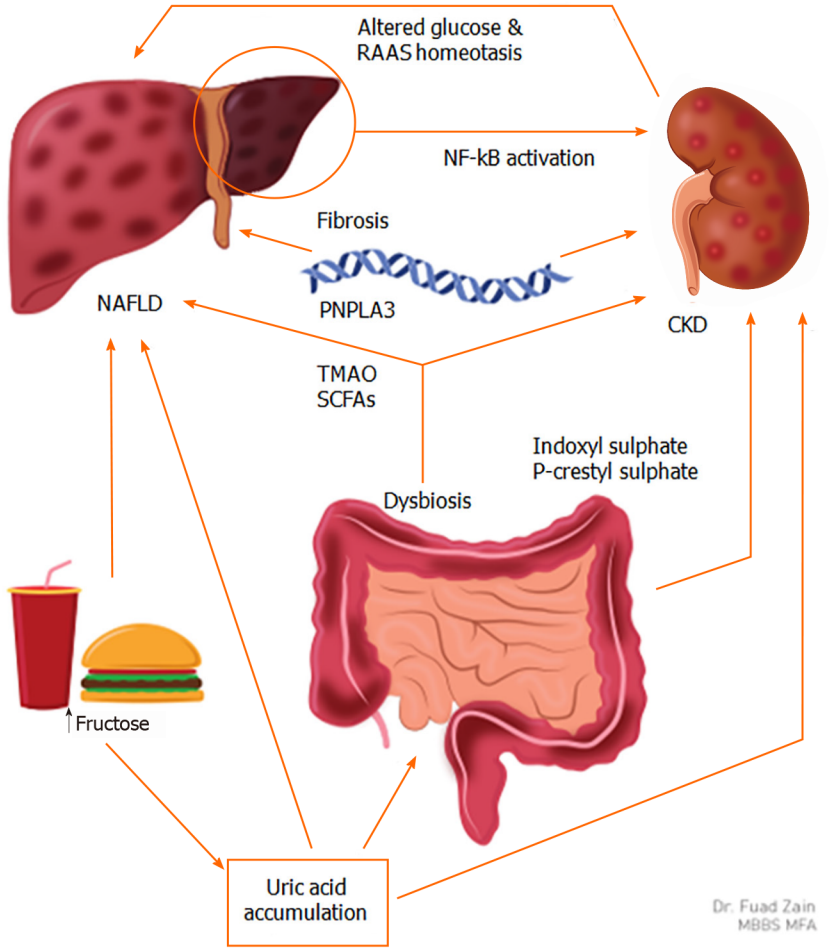


**Figure 2 Fructose consumption and uric acid accumulation play a key role in patients with non-alcoholic fatty liver disease who develop chronic kidney disease.** TMAO: Trimethylamine N-oxide; SCFAs: Short-chain fatty acids; RAAS: Renin-angiotensin-aldosterone system; PNPLA3: Patatin-like phospholipase domain-containing protein 3; NAFLD: Non-alcoholic fatty liver disease; CKD: Chronic kidney disease; NF-κB: Nuclear factor-κB.

invasive parameters (*i.e.* liver biopsy).

*Managing the progression of CKD*

**Surveillance of comorbidities**: In general, we recommend patients with diabetes and NAFLD undergo frequent surveillance for underlying kidney dysfunction, more so than patients with diabetes only. Monitoring thyrotropin and thyroid hormone levels may have clinical utility when evaluating the risk of developing CKD in patients with NAFLD; however, future studies are needed to specifically address the risk of CKD in patients with NAFLD and hypothyroidism (Table 4).

### Body weight

**Waist-to-hip ratio:** Few studies have evaluated the impact of weight loss on the progression of CKD in patients with NAFLD. Recent studies have shown that a decrease in the waist-to-hip ratio (WHR) in patients with NAFLD decreases the risk of CKD development[43]. Serial monitoring of WHR may be beneficial in identifying patients with NAFLD at risk for CKD. A drawback to this finding is that a reduction in WHR does not differentiate between a reduction in visceral fat *vs* subcutaneous fat. Studies have shown that visceral fat, but not subcutaneous fat, is the key driver in NAFLD pathogenesis *via* increased insulin resistance[93]. However, with regards to reducing the risk of CKD, the significance of reducing visceral *vs* subcutaneous fat is not well-studied.

**Weight loss:** Data from a post-hoc analysis of a clinical trial involving 261 patients with NAFLD showed a statistically significant relationship between reduction in body weight and changes in eGFR (when calculated by CKD-Epidemiology collaboration and modification of diet in renal disease equations), even after adjusting for

**Table 4 Summary of Interventions for patients with nonalcoholic fatty liver disease and chronic kidney disease**

| Intervention | Ref. | Year | *n* | Findings | Recommendation |
|---|---|---|---|---|---|
| Decreasing WHR | Chon *et al*[43]. 12-yr prospective cohort | 2020 | 6137 | A decrease in the WHR of more than 5% in patients with NAFLD leads to a significantly reduced risk of CKD development, even in non-obese patients | Serial Monitoring WHR may be beneficial in identifying patients with NAFLD at risk of developing CKD and reduction can ameliorate the progression |
| Weight loss | Vilar-Gomez *et al*[94]. Post-hoc analysis | 2017 | 261 | Improvement in liver histology due to weight loss linked to improved renal outcomes, even after adjusting for medication profile, diabetes, and hypertension | Advocate for weight loss |
| SGLT2 Inhibitors | Shimizu *et al*[96]. RCT | 2019 | 57 | SGLT inhibitor (Dapagliflozin) improved liver steatosis in patients with T2DM and NAFLD and attenuates liver fibrosis in patients with NAFLD-related advanced fibrosis | Although data is not sufficient, consider using SGLT2 inhibitors in T2DM patients with NAFLD and CKD |
| | Perkovic *et al*[95]. CREDENCE trial | 2019 | 4401 | SGLT2 inhibitor (Canagliflozin) decreased the risk of renal failure in patients with T2DM and CKD | |
| GLP-1 | Armstrong *et al*[100]. LEAN trial | 2016 | 52 | Liraglutide led to weight loss, glycemic control, and histological resolution of NASH | GLP-1's in NASH is considered effective in improving components of MetS, however, long-term studies are needed to determine NASH-related outcomes |
| | Tuttle *et al*[101]. AWARD-7 trial | 2018 | 577 | Once-weekly dulaglutide is associated with reduced decline in eGFR, while being as effective as insulin in achieving glycemic control | GLP-1 is a safe option for patients with CKD and is associated with slower progression of CKD |
| Coenzyme Q10 | Farhangi *et al*[109] and Farsi *et al*[110]. RCT | 2014[109] and 2016[110] | 44[109] and 41[110] | 100 mg of oral CoQ10/d improve biochemical variables of NAFLD after 4 wk[109] and 12 wk[110] of treatment | Due to lack of data in patients with both NAFLD and CKD, the benefit of CoQ10 supplementation is unknown; however, in separate trials with regards to both NAFLD and CKD, CoQ10 supplementation is beneficial |
| | Yeung *et al*[111]. RCT | 2015 | 15 | Oral CoQ10 supplementation in patients with CKD showed significant improvement in serum creatinine when compared to placebo | |

WHR: Waist-to-hip ratio; NAFLD: Nonalcoholic fatty liver disease; CKD: Chronic kidney disease; SGLT2: Sodium-glucose co-transporter-2; RCT: Randomized controlled trial; T2DM: Type 2 Diabetes Mellitus; GLP-1: Glucagon-like peptide receptor agonist; NASH: Non-alcoholic steatohepatitis.

medication profile, diabetes, and hypertension[94]. Additionally, patients with improvement in liver histology due to lifestyle modifications such as weight loss were linked with significantly improved renal outcomes[94]**.** Overall, patients with NAFLD who had more than 5% weight loss and/or more than a 5% reduction in WHR had improved renal outcomes.

**Sodium-glucose cotransporter type-2 inhibitors:** In patients with T2DM, sodium-glucose cotransporter type-2 (SGLT2) inhibitors have an established role in improving glycemic control, weight loss, cardiovascular outcomes, and lowering serum uric acid levels. In patients with type 2 diabetes, the landmark CREDENCE trial showed that patients treated with an SGLT2 inhibitor (*i.e.*, canagliflozin) were shown to have improved outcomes related to CKD[95]. Furthermore, recent evidence has shown that SGLT2 inhibitors can also improve NAFLD progression as determined by TE[96] and biomarkers in NAFLD (*i.e.*, liver enzymes)[96,97]. As SGLT2 inhibitors decrease serum uric acid levels, this may also contribute to this class's positive effects on both diseases. In addition to facilitating glucosuria, SGLT2 inhibitors are thought to decrease inflammation and reactive oxygen species formation[98], which is key in the pathogenesis of NAFLD and NASH[99].

**Glucagon-like peptide 1 receptor agonists:** Among its multiple mechanisms of action, glucagon-like peptide 1 **(**GLP-1)'s aid in increasing insulin secretion, delaying gastric

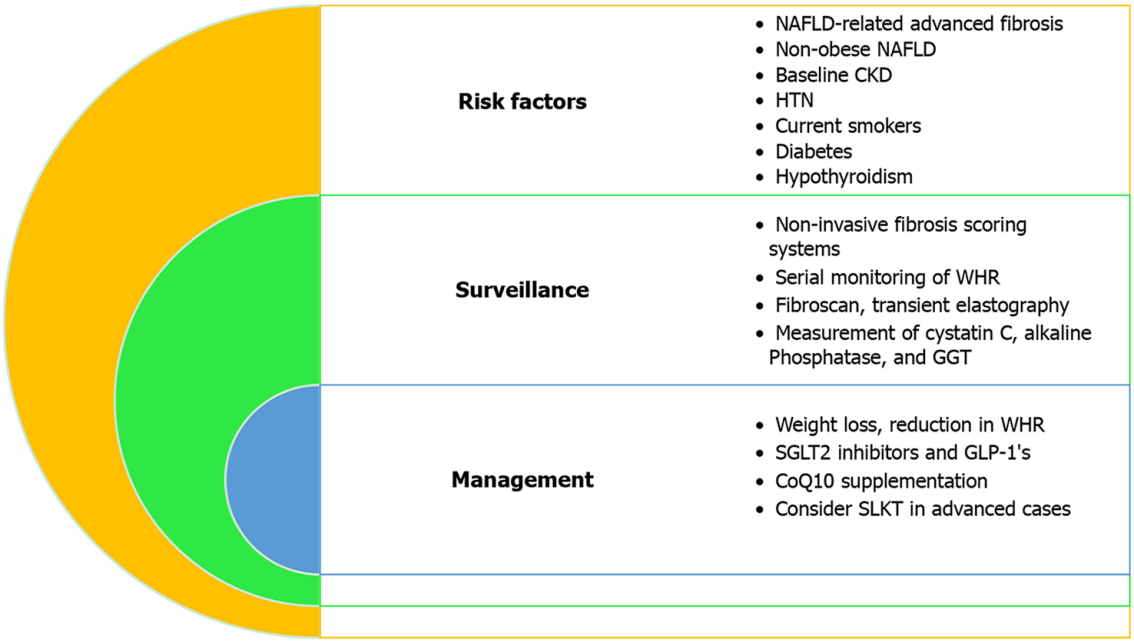


**Figure 3 Identifying and managing non-alcoholic fatty liver disease patients who are at risk for developing chronic kidney disease.**
NAFLD: Non-alcoholic fatty liver disease; CKD: Chronic kidney disease; HTN: Hypertension; WHR: Waist-to-Hip ratio; GGT: Gamma-glutamyl transferase; T2DM: Type 2 diabetes mellitus; SLKT: Simultaneous liver-kidney transplantation; SGLT2: Sodium-glucose cotransporter type-2; GLP-1: Glucagon-like peptide 1.

emptying, and decreasing appetite, all of which can lead to improved glycemic control and weight loss. Additionally, a possible anti-inflammatory mechanism makes GLP-1's an attractive agent in NAFLD and NASH. For instance, GLP-1 Liraglutide, when compared to placebo, led to histological resolution of NASH; however, larger studies are still needed[100]. In CKD, GLP-1's are shown to be nephroprotective, which could be due to GLP-1's ability to lower blood pressure in addition to the aforementioned mechanisms[101,102]. GLP-1's and SGLT2 inhibitors exhibit cardioprotective effects, and as discussed previously, patients with NAFLD and CKD are at high risk for CV events. Therefore, the use of these agents is recommended in patients with NAFLD and CKD. However, while there is landmark data to support the use of GLP-1's and SGLT2 inhibitors to prevent CV events in patients with established CVD, data on primary prevention in patients with NAFLD and CKD is lacking[103,104]. Regardless, in patients with T2DM, CKD, and NAFLD, SGLT2 inhibitors or GLP-1's are highly recommended not only for glycemic control but for the cardio-, hepato-, and nephro-protective effects as well.

**Coenzyme Q10:** Coenzyme Q10 (CoQ10) is produced endogenously and has antioxidant and anti-inflammatory effects[105]. CoQ10 also serves as an electron carrier in cellular respiration and a cofactor in pyrimidine synthesis for DNA repair and replication, among other important roles. Patients with NAFLD, CKD, and/or CVD have been reported to have CoQ10 deficiency[106]. A majority of endogenous CoQ10 is produced in the liver, and patients with NAFLD had diminished CoQ10 production[106,107]. CoQ10 deficiency will lead to oxidative stress, which plays a key pathogenic factor in NAFLD[108]. Results from separate trials assessing oral CoQ10 supplementation in patients with NAFLD and CKD are summarized in Table 4. Briefly, CoQ10 has been shown to improve NAFLD parameters and CKD parameters in separate trials[109-111]. Specific findings are summarized in Table 4. CoQ10 has positive effects on the progression of CVD as well, which is notable because patients with CKD and NAFLD are at risk for cardiovascular events[112,113]. Supplementation may be beneficial in patients with NAFLD who have CKD, but clinical data in this population is lacking.

### *Experimental interventions*

**Thiazolidinediones:** Thiazolidinediones are agonists of peroxisome proliferator-activated receptors (PPARs), and they play a physiologic role in metabolism and cellular differentiation. PPARs have proven clinical utility in diseases such as hyperlipidemia (PPARα) and T2DM (PPARγ)[114]. Because CKD is a manifestation of a

metabolic and/or inflammatory process, the use of PPAR agonists has been studied in patients with CKD. Specifically, pioglitazone, a PPARγ agonist, has been shown to improve cardiovascular outcomes in patients with CKD and diabetes[115]. Several RCTs have shown the beneficial effects that pioglitazone has on histopathology and metabolic function in patients with NASH[116-120]. Pioglitazone has been endorsed as a pharmacological agent in biopsy-proven NASH by the American Association for the Study of Liver Diseases[121]. Rosiglitazone has been shown to improve histological components of NASH through increasing insulin sensitivity[122] while also improving liver function[123] in a separate study, although both studies did not show improvements in liver fibrosis[122,123]. Interestingly, an extension trial showed that rosiglitazone was only beneficial in the first year of treatment, without substantial benefit noted with longer use[124]. However, Rosiglitazone is not available in most countries and its use is limited in the United States due to data concerning for increased coronary events. The most widely studied PPAR agonist, Pioglitazone has shown favorable outcomes in patients with CKD and patients with NAFLD, but data assessing the efficacy in patients with both CKD and NAFLD is lacking[114].

**Vitamin D:** Vitamin D deficiency is associated with increased severity of NAFLD[125] and is also associated with CKD[126]. These findings may be explained by the physiology of vitamin D activation, which requires hydroxylation by both the kidney and liver, and therefore the presence of CKD and NAFLD inevitably leads to vitamin D resistance[58]. Furthermore, experimental models have demonstrated the role hypovitaminosis D plays in the pathogenesis of both CKD and NAFLD[58]. In patients with CKD, therapeutic implications of higher vitamin D supplementation showed an ability to correct hypovitaminosis D[127], but a meta-analysis yielded a higher incidence of hypercalcemia[128]. In patients with NAFLD, vitamin D supplementation did not correct hypovitaminosis D[129], however, trials are underway for assessing the use of Vitamin D supplementation in CKD and NAFLD/NASH[130-132] (NCT00893451, NCT01623024, and NCT02098317, www.clinicaltrials.gov).

**Probiotics**: In rodent models, fecal microbiota transplantation[133], antibiotics in fructose-fed models[134] reduced NAFLD severity, whereas specific probiotics (*Lactobacillaceae* or *Bifidobacteriales*) alleviated proteinuria and reduced systemic inflammation in rodents with CKD. While much of this data is based on studies from animal models, human trials are needed to further evaluate the therapeutic implications of the gut-liver-kidney axis.

### *LT for patients with NAFLD/NASH and CKD*

In recent decades, NASH has become more prevalent and will become the most common indication for LT[135]. Patients with NASH have a higher incidence of CKD compared with other etiologies, and therefore, NASH is rapidly growing as a cause for not only LT[136,137] but also simultaneous liver-kidney transplantation (SLKT) in the United States given serum creatinine and dialysis status are important components of the model for end-stage liver disease (MELD) score[138]. Considering the increased incidence of renal dysfunction at LT due to prioritization based on the MELD allocation system in the United States, SLKT rates climbed from 2.7% of all LT in 2000 to 9.3% in 2016[138-140]. NASH is currently the leading and most rapidly growing indication for SLKT in the United States[138,140] with a 200% increase for SLKT from 2002 to 2010[138]. Patients with NASH have a high probability to undergo SLKT rather than LT alone since they are highly incident for CKD for a prolonged duration, which can fulfill criteria for SLKT (patients with CKD: GFR ≤ 60 mL/min for ≥ 3 mo with recent GFR ≤ 30 mL/min or on hemodialysis, patients with AKI: Dialysis for > 6 wk GFR ≤ 25 for > 6 wk)[141].

Patients with NASH were independently associated with a higher risk of CKD or advanced kidney damage after LT compared with those without NASH[142-144]. In general, renal dysfunction after LT is affected not only by immunosuppressant medications, especially calcineurin inhibitors, pre-LT kidney dysfunction, but also persistent or de novo metabolic co-morbidities such as hypertension, diabetes, and obesity - all of which are highly likely in NASH patients undergoing LT[142,145]. Special attention to the recognition of CKD is needed for patients with NASH patients when deciding LT *vs* SLKT. Controlling for metabolic complications and avoiding or keeping a low dose of calcineurin inhibitors as much as possible seems to be crucially important to reduce the risk of incident CKD, and risk of progression of CKD after liver transplant in NASH patients.

## CONCLUSION

Despite the breadth of research, minimal guideline-based management of patients with both NAFLD and CKD is available. However, important pathogenic links and shared risk factors between NAFLD and CKD underscore the importance of earlier surveillance and strict control of shared metabolic risk factors. Although preventative strategies for CKD in NAFLD are limited, treatment directed specifically for NASH in the future will hopefully ameliorate the progression of renal dysfunction in affected patients. There is a plethora of clinical trials underway, and if these drugs show safety and efficacy in improving NASH, they may translate into improving renal function[146]. Specific interventions for preventing CKD progression using SGLT2 inhibitors, PPAR agonists, SAM, XO inhibitors, and Vitamin D have been tried but need further confirmation. Progression from NAFLD to NAFLD-related advanced fibrosis is linked to an increased risk of CKD, and earlier intervention in those with renal dysfunction is warranted. Genetic links between NAFLD and CKD have also been proposed, specifically in the G allele of *PNPLA3* and the T allele of *TM6SF2*, and future studies targeting patients with such genetic profiles to prevent progression to CKD is needed.

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