Risk of chronic kidney disease in patients with non-alcoholic fatty liver disease: Is there a link?

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Non-alcoholic fatty liver disease (NAFLD) has emerged as a growing public health problem worldwide. Increasing recognition of the importance of NAFLD and its association with the features of the metabolic syndrome has stimulated an interest in its putative role in the development and progression of chronic kidney disease (CKD). Accumulating evidence suggests that NAFLD and CKD share many important cardio-metabolic risk factors and common pathogenetic mechanisms and that NAFLD is associated with an increased prevalence and incidence of CKD. This association appears to be independent of obesity, hypertension, and other potentially confounding factors, and it occurs both in patients with diabetes and in those with diabetes. Although further research is needed to establish a definitive conclusion, these observations raise the possibility that NAFLD is not only a marker of CKD but also might play a part in the pathogenesis of CKD, possibly through the systemic release of several pro-inflammatory/pro-coagulant mediators from the steatotic/inflamed liver or through the contribution of NAFLD itself to insulin resistance and atherogenic dyslipidemia. However, given the heterogeneity and small number of observational longitudinal studies, further research is urgently required to corroborate the prognostic significance of NAFLD for the incidence of CKD, and to further elucidate the complex and intertwined mechanisms that link NAFLD and CKD. If confirmed in future large-scale prospective studies, the potential adverse impact of NAFLD on kidney disease progression will deserve particular attention, especially with respect to the implications for screening and surveillance strategies in the growing number of patients with NAFLD.

Introduction

Chronic kidney disease (CKD) is a worldwide health problem that results in high morbidity, mortality, and health care costs. CKD is defined as a sustained reduction in the glomerular filtration rate (GFR) or evidence of structural or functional abnormalities of the kidneys based on urinalysis, biopsy, or imaging [1,2]. Recent data from the United States population-based Third National Health and Nutrition Examination Survey (NHANES III) reported that the prevalence of CKD in the United States is approximately 13% [3]. In Europe, the prevalence of CKD is very similar to that in the United States [1,4]. CKD has many potential causes, which vary in frequency between different populations. In developed countries, older age, hypertension, diabetes, obesity, and dyslipidemia are consistently associated with CKD [1,2,4–8]. Notably, CKD is increasingly recognized as a major risk factor not only for end-stage renal disease but also for cardiovascular disease (CVD) [2,9,10].

Non-alcoholic fatty liver disease (NAFLD) has reached epidemic proportions and is the most common cause of chronic liver disease in Western countries [11–13]. It comprises a disease spectrum ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis. NAFLD is strongly associated with a myriad of important co-morbidities, such as obesity, diabetes, hypertension, and atherogenic dyslipidemia, and it is now regarded as the hepatic manifestation of the metabolic syndrome [11–13]. The prevalence of NAFLD has been estimated to be between 20% and 30% in the general adult population in Western countries but this value is much higher among persons who are obese or have diabetes [11–15].

In recent years, the recognition of the importance of NAFLD and its strong relationship with clinical traits of the metabolic syndrome has stimulated a growing interest in the potential prognostic value of NAFLD for adverse CVD outcomes [14]. Similarly, the possible link between NAFLD and CKD has also attracted scientific interest. NAFLD and CKD share many important cardio-metabolic risk factors and common pathogenetic mechanisms, and both are linked to an increased risk of incident CVD events [2,9,10,13,14]. Moreover, the presence of pathophysiological inter-relationships between the liver and the kidney is well established in humans, and is supported by the presence of the
Increased prevalence of risk factors of chronic kidney disease in patients with NAFLD

Patients with NAFLD, both adults and children, frequently meet the diagnostic criteria for the metabolic syndrome (i.e., obesity, hypertension, atherogenic dyslipidemia, and dysglycemia) and, therefore, have multiple risk factors for CVD [11–15].

Patients with NAFLD also have greater insulin resistance than control subjects who do not have steatosis, and there is a near-universal association between NAFLD and insulin resistance, irrespective of obesity [11–14]. Although NAFLD is now regarded as the hepatic manifestation of the metabolic syndrome [11–14], it is important to note that not all patients with the metabolic syndrome will develop NAFLD and not all patients with NAFLD have the metabolic syndrome. This may also have clinical implications in terms of CVD risk assessment in NAFLD given that the concept of the metabolic syndrome and its prognostic importance for CVD outcomes have repeatedly been challenged. In particular, there remains debate as to whether or not the prognostic significance of the metabolic syndrome exceeds the risk associated with the sum of its individuals components [16,17].

As reviewed in detail elsewhere [18,19], a number of case-control studies have also shown that NAFLD is associated with many other emerging and non-traditional CVD risk factors. As compared with control subjects who do not have steatosis, patients with NAFLD have significantly lower plasma adiponectin levels, higher plasma inflammatory and hemostatic factors, and higher plasma endothelial dysfunction, and oxidative stress biomarkers [13–15,18,19].

Several epidemiological studies have shown that the classical CVD risk factors, such as obesity, diabetes, hypertension, and dyslipidemia, are also important risk factors for the development and progression of CKD [1,2,5–8]. Recently, in the Atherosclerosis Risk in Communities (ARIC) study, it has also been reported that the metabolic syndrome is associated with an increased risk for incident CKD over a 9-year period [20]. This risk was independent of potential confounding factors such as age, sex, race, education, body mass index, alcohol and tobacco use, pre-existing CVD, and physical activity. There were strong, graded relationships among the number of clinical traits of the metabolic syndrome, HOMA-insulin resistance, or fasting insulin levels and the risk for incident CKD, suggesting a pathophysiological basis for these findings. Moreover, the increased risk for CKD was evident even after adjusting for hypertension (a potential cause and consequence of kidney disease) and incident diabetes (another known mediator of CKD) [20]. These observations provide a rationale for intervention studies that aim to verify whether treating the many features of the metabolic syndrome can effectively prevent the development and progression of renal damage.

Finally, and similarly to the associations observed in NAFLD, a number of observational studies have indicated that CKD is associated with decreased adiponectin levels, increased oxidative stress, elevated systemic inflammation, hypercoagulation, and hypofibrinolysis [5,21–23]. Although most of the human studies performed to date are observational, and, therefore, causal relationships cannot be definitively determined, many of these emerging risk factors and biomarkers could potentially be implicated in the development and progression of CKD [5,21–23].

Increased prevalence of chronic kidney disease in patients with NAFLD

Several investigators [24–34] have examined the prevalence of kidney disease in patients with NAFLD (as described in Table 1). Given the strong association between NAFLD and multiple risk factors for CKD, it is certainly not surprising that patients with NAFLD have a remarkably higher prevalence of CKD than do control subjects without steatosis.

In a large community-based cohort involving approximately 2000 unselected patients with type 2 diabetes, the prevalence of CKD (defined as estimated GFR < 60 ml/min/1.73 m² or overt proteinuria) was higher among patients with ultrasound-diagnosed NAFLD than among those without this disease (15% vs. 9%, p < 0.001), independently of traditional risk factors, duration of diabetes, extent of glycemic control, use of lipid-lowering, hypoglycemic, anti-hypertensive, and anti-platelet medications, and components of the metabolic syndrome [24]. The findings were similar in a study of adults with type 1 diabetes [25].

In 1361 patients who presented an abnormal oral glucose tolerance test on routine screening, patients with ultrasound-diagnosed NAFLD had a greater prevalence of microalbuminuria compared with those who did not have steatosis (19% vs. 6.3% in patients with pre-diabetes; 32.6% vs. 4.5% in those with newly diagnosed diabetes; p < 0.0001) [26]. Multivariate logistic regression analysis revealed that NAFLD was associated with the presence of microalbuminuria independently of several potential confounders [26].

Large population-based studies that used elevated serum liver enzyme levels as surrogate markers for NAFLD (and should therefore be interpreted with caution) have shown that this disease is independently associated with an increased prevalence of CKD [27–29]. For instance, data from the NHANES III study reported that mildly elevated levels of serum gamma-glutamyltransferase (GGT) were associated with an increased prevalence of CKD in the United States adult population after adjusting for demographics, co-morbidities, alcohol consumption, lipid-lowering medications, viral hepatitis status, and laboratory measures [27]. These findings are at variance with those reported in the Framingham Heart Study where serum creatinine levels did not change significantly across serum GGT quartiles [30]. However, it is important to note that estimated GFR is widely accepted as the best overall measure of kidney function, and that the use of serum creatinine alone, to distinguish differences across kidney function levels, can be misleading [4].

Among the few and small studies that used liver biopsy to diagnose NAFLD [31–34], Yilmaz et al. demonstrated that microalbuminuria was independently associated with the histologic features of NAFLD in a hospital-based sample of 87 nondiabetic individuals with NAFLD; however, their study lacked a control group [31]. Manco et al. failed to detect any significant differences in markers of kidney function between overweight/obese children with NAFLD and age- and sex-matched control children.
### Table 1. Principal cross-sectional studies of the association between NAFLD and chronic kidney disease.

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Study population</th>
<th>Diagnosis of NAFLD</th>
<th>Study measures</th>
<th>Adjustments considered</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targher G et al. [24]</td>
<td>Community-based cohort of 2,103 type 2 diabetic outpatients who did not have cardiovascular disease, cirrhosis or viral hepatitis</td>
<td>Ultrasonography</td>
<td>Estimated GFR ≤60 ml/min/1.73 m² or overt proteinuria</td>
<td>Age, sex, BMI, waist circumference, hypertension, alcohol consumption, diabetes duration, hemoglobin A\textsubscript{1c}, LDL-cholesterol, triglycerides, smoking, medication use (hypoglycemic, anti-hypertensive, anti-platelet or lipid-lowering drugs)</td>
<td>NAFLD associated with increased risk of prevalent CKD Adjusted OR 1.87 (1.3-4.1)</td>
</tr>
<tr>
<td>Targher G et al. [25]</td>
<td>202 type 1 diabetic adults who did not have secondary causes of chronic liver disease</td>
<td>Ultrasonography</td>
<td>Estimated GFR ≤60 ml/min/1.73 m² or urinary alb/creat ratio ≥30 mg/g</td>
<td>Age, sex, BMI, systolic blood pressure, alcohol consumption, diabetes duration, hemoglobin A\textsubscript{1c}, triglycerides, and medication use</td>
<td>NAFLD associated with increased risk of prevalent CKD Adjusted OR 3.29 (1.2-9.1)</td>
</tr>
<tr>
<td>Hwang ST et al. [26]</td>
<td>Health-examination survey of 1,361 patients with impaired glucose tolerance or newly diagnosed diabetes (on oral glucose tolerance test) who did not have cardiovascular disease, malignancy, cirrhosis and viral hepatitis</td>
<td>Ultrasonography</td>
<td>Urinary alb/creat ratio ≥30 mg/g</td>
<td>Age, sex, BMI, waist circumference, smoking, hemoglobin A\textsubscript{1c}, triglycerides, LDL-cholesterol, liver enzymes, insulin resistance, and presence of metabolic syndrome</td>
<td>NAFLD associated with increased risk of prevalent microalbuminuria Adjusted OR 3.66 (1.3-10.2) in patients with pre-diabetes Adjusted OR 5.47 (1.01-29.6) in those with newly diagnosed diabetes</td>
</tr>
<tr>
<td>Targher G et al. [27]</td>
<td>National Health and Nutrition Examination Survey (NHANES) 2001-2006; n = 13,188 men and women</td>
<td>Liver enzymes (serum GGT)</td>
<td>Estimated GFR &lt;60 ml/min/1.73 m² or alb/creat ratio n≥30 mg/g</td>
<td>Age, sex, race, smoking, alcohol intake, lipid-lowering medications, hypertension, diabetes, BMI, waist circumference, LDL-cholesterol, HDL-cholesterol, triglycerides, glucose, alanine aminotransferase, viral hepatitis status</td>
<td>Elevated serum GGT levels associated with prevalent CKD Adjusted OR 1.44 (1.2-1.74) for subjects with GGT levels in the 4\textsuperscript{th} quartile (i.e., GGT &gt;39 U/L for men and GGT &gt;25 U/L for women)</td>
</tr>
<tr>
<td>Targher G et al. [28]</td>
<td>National Health and Nutrition Examination Survey (NHANES) 2001-2006; n = 13,184 men and women</td>
<td>Liver enzymes (serum bilirubin)</td>
<td>Estimated GFR &lt;60 ml/min/1.73 m² or alb/creat ratio ≥30 mg/g</td>
<td>Age, sex, race, BMI, waist circumference, smoking, alcohol intake, lipid-lowering medications, hypertension, diabetes, LDL-cholesterol, HDL-cholesterol, triglycerides, insulin resistance, viral hepatitis status</td>
<td>Increased total bilirubin associated with abnormal albuminuria Adjusted OR 1.26 (1.03-1.54)</td>
</tr>
<tr>
<td>Yun KE et al. [29]</td>
<td>Health-examination survey of 37,085 Korean men and women without viral hepatitis and excessive alcohol consumption</td>
<td>Liver enzymes (serum ALT)</td>
<td>Estimated GFR</td>
<td>No adjustments</td>
<td>Subjects with serum ALT &gt;40 U/L had lower estimated GFR than those with serum ALT ≤40 U/L</td>
</tr>
<tr>
<td>Lee DS et al. [30]</td>
<td>Framingham Heart Study; n = 3,451 men and women</td>
<td>Liver enzymes (serum GGT)</td>
<td>Serum creatinine</td>
<td>No adjustments</td>
<td>No differences</td>
</tr>
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without steatosis [32]. Recently, we found that patients with histologically defined NASH had moderately decreased estimated GFR values and a greater frequency of both abnormal albuminuria and CKD than did matched control subjects who did not have steatosis. Notably, as shown in Fig. 1, the histologic severity of NASH (i.e., NASH/fibrosis stage) was associated with decreasing mean values of estimated GFR independently of traditional CVD risk factors, insulin resistance, and metabolic syndrome components [34]. Larger studies will be needed to confirm the reproducibility of these results.

Collectively, the published data provide clear evidence that NAFLD/NASH is associated with a greater prevalence of CKD, and suggest that NAFLD patients should be considered at increased risk for the development of CKD. However, the cross-sectional nature of these studies necessitates caution in interpreting the results, and large prospective studies are needed to determine whether NAFLD may contribute to the development and progression of CKD.

### Increased incidence of chronic kidney disease in patients with NAFLD

The main large prospective studies [35–38] assessing the relationship between NAFLD (as detected by means of ultrasonography or serum liver enzyme measurements) and the incidence of CKD are described in Table 2.

The Valpolicella Heart Diabetes Study enrolled 1760 type 2 diabetic individuals with normal or near-normal kidney function who did not have CVD, cirrhosis and viral hepatitis at baseline. During a mean follow-up of 6.5 years, 547 participants developed CKD.

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Study population</th>
<th>Diagnosis of NAFLD</th>
<th>Study measures</th>
<th>Adjustments considered</th>
<th>Main results and risk for prevalent CKD in subjects with NAFLD versus those without — odds ratios (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Yilmaz Y et al. [31]</td>
<td>Hospital-based sample of 87 NAFLD patients</td>
<td>Biopsy</td>
<td>24 hrs urinary albumin excretion rate</td>
<td>Age, sex, BMI, blood pressure, triglycerides, HDL-cholesterol, aminotransferases, insulin resistance</td>
<td>Microalbuminuria associated with the severity of NAFLD histology (i.e., fibrosis stage)</td>
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<tr>
<td>Manco M et al. [32]</td>
<td>80 overweight/obese children with NAFLD and 59 age- and sex-matched children</td>
<td>Biopsy</td>
<td>Creatinine clearance and 24 hr urinary albumin excretion rate</td>
<td>No adjustments</td>
<td>No differences</td>
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<td>Yasui K et al. [33]</td>
<td>Hospital-based sample of 174 NAFLD</td>
<td>Biopsy</td>
<td>Estimated GFR &lt;60 ml/min/1.73 m² or alb/creat ratio ≥30 mg/g</td>
<td>Age, sex, BMI, hypertension</td>
<td>NASH patients had higher frequency of CKD than those with simple steatosis. The association was primarily mediated by hypertension</td>
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<tr>
<td>Targher G et al. [34]</td>
<td>80 patients with NASH and 80 age-, sex- and BMI-matched control subjects without steatosis</td>
<td>Biopsy</td>
<td>Estimated GFR ≤60 ml/min/1.73 m² or alb/creat ratio ≥30 mg/g</td>
<td>Age, sex, BMI, waist circumference, smoking, blood pressure, triglycerides, insulin resistance</td>
<td>NASH patients had lower estimated GFR and higher frequency of CKD Adjusted OR 6.14 (1.6-12.8)</td>
</tr>
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</table>

ALT, alanine aminotransferase; BMI, body mass index; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein; LDL, low density lipoprotein; Alb, albumin; Creat, creatinine. Insulin resistance was estimated by a homeostasis model assessment (HOMA). Glomerular filtration rate (GFR) was estimated by using the Modification of Diet in Renal Disease (MDRD) study equation.

**Fig. 1.** Adjusted means (±standard deviations) of estimated glomerular filtration rate (GFR) in relation to the histologic severity of non-alcoholic steatohepatitis (i.e., NASH/fibrosis stage increasing from zero to three) in patients with NASH. p value for the trend is determined by means of analysis of covariance. Data have been adjusted for age, sex, body mass index, waist circumference, hypertension status, levels of triglycerides, and insulin resistance (as estimated by homeostasis model assessment). Data are from Targher et al. [34].

Table 1 (continued)

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ALT, alanine aminotransferase; BMI, body mass index; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein; LDL, low density lipoprotein; Alb, albumin; Creat, creatinine. Insulin resistance was estimated by a homeostasis model assessment (HOMA). Glomerular filtration rate (GFR) was estimated by using the Modification of Diet in Renal Disease (MDRD) study equation.
incident CKD (defined as estimated GFR <60 ml/min/1.73 m² or overt proteinuria). Multivariate logistic regression analysis revealed that ultrasound-diagnosed NAFLD was associated with an increased incidence of CKD, independently of a broad number of important risk factors and potential confounders [35].

Similarly, Chang et al. [36] followed a community-based cohort of 8329 healthy Asian men with normal kidney function and no proteinuria at baseline for a mean period of 3.5 years. During the follow-up, 324 individuals developed incident CKD (i.e., estimated GFR <60 ml/min/1.73 m² or overt proteinuria). Ultrasound-diagnosed NAFLD was associated with an increased risk of incident CKD independently of traditional risk factors, insulin resistance, metabolic syndrome components or C-reactive protein [36].

Table 2. Principal prospective studies of the association between NAFLD and the incidence of chronic kidney disease.

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Study population</th>
<th>Length of follow-up (years)</th>
<th>Diagnosis of NAFLD</th>
<th>Study outcomes</th>
<th>Adjustments considered</th>
<th>Main Results and Risk for incident CKD in subjects with NAFLD versus those without — hazard ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targher G et al.</td>
<td>Ultrasound-diagnosed NAFLD in patients with normal kidney function and no overt proteinuria at baseline</td>
<td>6.5</td>
<td>Ultrasonography</td>
<td>Estimated GFR &lt;60 ml/min/1.73 m² or overt proteinuria</td>
<td>Sex, age, BMI, waist circumference, blood pressure, smoking, diabetes duration, hemoglobin A1c, triglycerides, HDL-cholesterol, LDL-cholesterol, estimated GFR, medication use (i.e. lipid-lowering, hypoglycaemic, anti-hypertensive, anti-platelet drugs)</td>
<td>NAFLD associated with increased risk of incident CKD Adjusted HR 1.49 (1.1-2.2)</td>
</tr>
<tr>
<td>Chang Y et al.</td>
<td>Community-based cohort of 10,337 healthy non-diabetic and non-hypertensive men with normal kidney function</td>
<td>3.2</td>
<td>Ultrasonography</td>
<td>Estimated GFR &lt;60 ml/min/1.73 m² or overt proteinuria</td>
<td>Age, BMI, alcohol consumption, blood pressure, smoking, fasting glucose, estimated GFR, triglycerides, HDL-cholesterol, LDL-cholesterol, insulin resistance or C reactive protein</td>
<td>NAFLD associated with increased risk of incident CKD Adjusted HR 1.60 (1.27-2.01)</td>
</tr>
<tr>
<td>Lee DH et al.</td>
<td>Coronary Artery Risk Development in Young Adults (CARDIA) study: n = 2,478 black and white men and women</td>
<td>15</td>
<td>Liver enzymes (serum GGT)</td>
<td>Urinary alb/creat ratio ≥30 mg/g</td>
<td>Age, sex, race, study center, education, BMI, smoking, alcohol consumption, physical exercise, hypertension, diabetes, triglycerides, HDL-cholesterol, LDL-cholesterol</td>
<td>Elevated serum GGT levels associated with increased risk of incident microalbuminuria Adjusted HR 4.38 (1.48-12.9) for subjects with GGT levels in the 4th quartile (i.e., ≥29 U/L)</td>
</tr>
<tr>
<td>Ryu S et al.</td>
<td>Community-based cohort of 10,337 non-diabetic and non-hypertensive men with normal kidney function and no proteinuria at baseline</td>
<td>2.5</td>
<td>Liver enzymes (serum GGT)</td>
<td>Estimated GFR &lt;60 ml/min/1.73 m² or overt proteinuria</td>
<td>Age, BMI, alcohol intake, blood pressure, smoking, triglycerides, HDL-cholesterol, LDL-cholesterol, uric acid, estimated GFR, insulin resistance or C reactive protein</td>
<td>Elevated serum GGT levels associated with increased risk of incident CKD Adjusted HR 1.87 (1.31-2.67) for subjects with GGT levels in the 4th quartile (i.e., &gt;40 &gt;40 U/L)</td>
</tr>
</tbody>
</table>

BMI, body mass index; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein; LDL, low density lipoprotein.

Insulin resistance was estimated by a homeostasis model assessment (HOMA). Glomerular filtration rate (GFR) was estimated by using the Modification of diet in renal disease (MDRD) study equation.
Two large prospective studies using elevated serum liver enzyme levels as surrogate markers for NAFLD have also shown that this disease was independently associated with an increased incidence of kidney disease [36,37]. For instance, in the Coronary Artery Risk Development in Young Adults (CARDIA) study serum GGT levels showed a positive dose–response association with incident microalbuminuria among individuals who had ever been diagnosed with hypertension or diabetes during 15 years of the study [37].

It is important to note that the patient cohorts (diabetic in one, nondiabetic in three) and the definition of NAFLD used in the four published prospective studies were heterogeneous and that the individual outcome measures were not uniform (GFR reduction or overt proteinuria in three, microalbuminuria in one), as specified in Table 2. Moreover, in all these studies, the authors used an estimated GFR instead of direct GFR measurement to define CKD. It is known that the Modification Diet in Renal Disease (MDRD) study equation underestimates renal function in severely obese subjects and demonstrates a greater inaccuracy in populations without known CKD (or in patients with early stages of CKD) than in those with kidney disease (i.e., patients with stages 3–5 of CKD) [1,2,4]. Nonetheless, current GFR estimates facilitate the evaluation and management of CKD, and many scientific organizations recommend the use of the MDRD study equation to estimate kidney function in epidemiologic studies and in clinical practice [2,3,9]. Moreover, the diagnosis of NAFLD was based on either serum liver enzymes or ultrasound imaging but was not confirmed by liver biopsy, which is the gold standard for the diagnosis of NAFLD [11–14]; however, it would be unacceptable to perform routine liver biopsies in large epidemiologic studies. Finally, the four published prospective studies employed varying degrees of baseline adjustments for risk factors of CKD as specified in Table 2. In particular, only a few of these studies adjusted their results for important risk factors such as abdominal obesity or insulin resistance, which play important roles in the pathogenesis of NAFLD and CKD. An accurate assessment of abdominal visceral fat and insulin resistance would be particularly important to better understand whether the relationship between CKD and NAFLD is affected by these two risk factors.

Despite these limitations, the data from the published prospective studies seem to be in favor of a significant association between NAFLD and the risk of incident CKD. However, uncertainty remains as to whether NAFLD poses an independent risk above and beyond known risk factors. There is a suggestion in that direction, but studies are too few and methodologically not rigorous. Additional large-scale prospective studies of a more extensive panel of known risk factors are needed to draw a firm conclusion about any independent hepatic contribution to the increased risk of CKD observed among patients with NAFLD. Moreover, because CKD has many potential causes, it will also be of great interest to define whether NAFLD may selectively contribute to the pathogenesis of different types of kidney disease.

**Putative biological mechanisms linking NAFLD and chronic kidney disease**

As described in a previous section of the article, because CKD and NAFLD share many important cardio-metabolic risk factors, it is perhaps not surprising that the two diseases are closely associated with one another. Understanding the complex and intertwined mechanisms that link NAFLD and CKD is important not only because of the societal health burden of both diseases but also because novel insights into the underlying mechanisms may lead to new strategies to prevent or treat CKD and its associated co-morbidities. The presence of pathophysiologic interrelationships between the liver and the kidney is well established in humans, and is supported by the presence of the hepatorenal syndrome, which is characterized by the occurrence of rapid and progressive renal impairment in patients with decompensated cirrhosis [40]. From a pathophysiologic perspective, there are at least two key questions that should be addressed. First, is NAFLD associated with CKD as a consequence of the shared cardio-metabolic risk factors, or does NAFLD itself contribute to the development of CKD independently of these factors? Second, is the risk of CKD also increased in patients with simple steatosis, or is the necroinflammation characteristic of NASH a necessary “nephro-toxic” stimulus?

Although CKD and NAFLD share common pathophysiologic mechanisms, the understanding of these overlapping pathways is presently incomplete. The close correlations of NAFLD and CKD with abdominal obesity and insulin resistance make it extremely difficult to distinguish the precise causal relationships underlying the increased risk of CKD among patients with NAFLD.

As schematically shown in Fig. 2, the putative underlying mechanisms that link NAFLD and CKD might originate from the expanded and inflamed visceral adipose tissue, with the liver functioning as both the target of the resulting systemic abnormalities and the source of several molecular mediators that amplify the kidney damage.

Expanded and inflamed visceral adipose tissue releases multiple molecules that are potentially involved in the development of insulin resistance and kidney damage, including hormones, free fatty acids (FFA), interleukin (IL)-6, tumor necrosis factor (TNF)-alpha, and other pro-inflammatory cytokines [41,42]. These adipocytokines may be derived from both the adipocytes themselves and/or from infiltrating macrophages [41,42]. The resulting adipose tissue inflammation is one of the earliest steps in the chain of events that leads to systemic insulin resistance, especially in obese and overweight persons [42,43]. Activation of pro-inflammatory pathways is mediated by cytokine receptors and pattern recognition receptors, including toll-like receptors and receptors for advanced glycation end products, which are gatekeepers of the innate immune system [42,43]. These pathways converge on two main intracellular transcription factor signaling pathways, namely, the nuclear factor-kB (NF-kB) pathway, which is activated by the inhibitor of NF-kB kinase beta, and the c-Jun N-terminal kinase (JNK) pathway [42,43]. Experimental findings in mice indicate that JNK-1 activation in adipose tissue may cause insulin resistance in the liver [44].

Fatty liver results from increased hepatic uptake of FFA derived mainly from the hydrolysis of adipose-tissue triglycerides (increased because of insulin resistance) but also from dietary chylomicrons and hepatic lipogenesis [11–13]. Insulin resistance is a key factor in the pathogenesis of NAFLD [11,13,45] and also plays a role in the development of CKD [5,20–23].

In the presence of increased FFA influx and chronic inflammation, the liver is again both the target of and the contributor to systemic inflammatory changes. Activation of the NF-kB pathway
in the liver of NASH patients leads to the increased transcription of several pro-inflammatory genes that amplify systemic chronic inflammation [43–45]. Fatty liver is associated with increased production of IL-6 and other pro-inflammatory cytokines by hepatocytes and non-parenchymal cells, including Kupffer cells and hepatic stellate cells [45,46]. The increase in intra-hepatic cytokine expression results from local activation of the NF-κB pathway, as mediated by hepato-cellular damage and fat-derived factors, and it is likely to play a role in the pathophysiology of NAFLD [43,45] and CKD [5,23].

The possible molecular mediators linking NAFLD and CKD may include the systemic release of several pathogenic factors from the steatotic/inflamed liver, such as increased reactive oxygen species, plasminogen activator inhibitor-1 (PAI-1), IL-6, C-reactive protein (CRP), TNF-alpha, transforming growth factor (TGF)-beta, and other pro-inflammatory cytokines (as summarized in Fig. 2). Notably, several case-control studies have shown that these plasma inflammatory, pro-coagulant, and oxidative stress factors are remarkably higher in patients with NAFLD/NASH than in those without those conditions [18,19,45–48]. From a pathophysiological perspective, it is important to emphasize that chronic inflammation, enhanced oxidative stress, and hypercoagulation are increasingly recognized for their role in the pathogenesis of CKD in animal models [23,49–51]. Consistent with the hypothesis that liver inflammation (or other liver-derived factors) in NAFLD may play a role in the pathogenesis of CKD, Cheng et al. reported that individuals with chronic hepatitis B virus infection were more likely to develop end-stage renal disease compared to those who were not infected with hepatitis B virus [52]. However, as previously reported, other pathophysiological mechanisms that are not strictly related to liver inflammation may contribute to the development of CKD in patients with NAFLD. Decreased concentrations of plasma adiponectin, an adipose-secreted cytokine with anti-diabetic and anti-inflammatory properties [53], might represent another potential mechanism that links NAFLD and CKD. Individuals with NAFLD exhibit significantly lower plasma adiponectin levels than do healthy controls without steatosis, and among persons with NAFLD, plasma adiponectin levels are inversely associated with the histologic severity of NAFLD independently of obesity and other underlying meta-

Fig. 2. Schematic representation of potentially causative mechanisms by which NAFLD may contribute to the development and progression of chronic kidney disease.
The increased rates of CKD and CVD are probably among the most important clinical features associated with NAFLD, and our knowledge concerning this phenomenon is rapidly evolving.

To date, there is a mounting body of evidence suggesting that patients with NAFLD have multiple risk factors of CKD and that NAFLD is associated with an increased prevalence and incidence of CKD both in patients without diabetes and in those with diabetes (as specified in Tables 1 and 2).

The underlying mechanisms and the biological plausibility of these findings remain speculative. The most plausible explanation for these findings is that the link between NAFLD and CKD may be represented by the shared cardio-metabolic risk factors and the similar pathogenetic mechanisms that link NAFLD and CKD. However, although further research in this area is needed to draw a definitive conclusion, the published data from recent prospective studies suggest that NAFLD is associated with an increased risk of incident CKD that is independent of the risk conferred by traditional risk factors and components of the metabolic syndrome. Collectively, these findings raise the possibility that NAFLD/NASH not only is a marker of CKD but also might contribute to its pathogenesis, possibly through the systemic release of several pathogenic mediators from the steatotic/inflamed liver or through the contribution of NAFLD itself to hepatic/systemic insulin resistance and atherogenic dyslipidemia (as summarized in Fig. 2).

The potential clinical implications of these findings for patient care are that the detection of hepatic steatosis (NAFLD) by routine ultrasound examination should alert clinicians to the possible coexistence of multiple risk factors of CKD and, therefore, warrant the evaluation and treatment of kidney disease equivalently to the risk for advancing liver disease.

NAFLD and CKD share similar treatment strategies, which are aimed primarily at reducing insulin resistance and modifying the associated cardio-metabolic risk factors [11,13,75,76]. Pharmacotherapy for NAFLD should probably be reserved for patients with NASH who are at highest risk for disease progression [11,13]. The lack of adequately powered randomized controlled trials of sufficient duration and with histological end-points makes it difficult to provide definitive recommendations regarding the treatment of NAFLD/NASH. Current recommendations are limited to weight reduction, through diet and physical exercise [75], and to the treatment of individual components of the metabolic syndrome with the use of therapies that may have beneficial hepatic effects, including bariatric surgery for obesity, insulin-sensitizing agents for type 2 diabetes, and drugs directed at the renin-angiotensin system for hypertension [11,13,76]. To date, there is no convincing evidence that lipid-lowering agents, including statins, are beneficial for NAFLD, although there is considerable evidence that statin therapy is safe [77]. Preliminary evidence also supports a role for anti-oxidants, anti-cytokine agents, and hepatoprotectants [11,76,78]; however, there are insufficient data to either support or refute the use of these agents as standard therapy for patients with NAFLD.

Despite the growing evidence that links NAFLD with CKD, it remains to be definitively established whether a causal association exists. Additional large-scale studies are needed to elucidate whether ameliorating NAFLD will ultimately prevent or slow the development and progression of CKD. Moreover, the prognostic importance of NAFLD in CKD risk stratification remains debatable. Thus, more research is urgently needed to corroborate a prognostic value of NAFLD for the incidence of CKD, and to

Conclusions

NAFLD is increasingly diagnosed worldwide and is the most common cause of chronic liver disease in Western countries [11–13].
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further elucidate the putative underlying mechanisms that link NAFLD and CKD.

In the interim, from the perspective of clinical practice, it is important that specialists and practicing clinicians be aware of the significant association between NAFLD and CKD, especially because of the high and growing prevalence of CKD and NAFLD. A multidisciplinary approach to the treatment of NAFLD patients, based on a careful evaluation of related risk factors and monitoring for cardiovascular, kidney, and liver complications, is warranted. In particular, health care providers who manage patients with NAFLD (especially those with more advanced stages of NAFLD) not only should focus on liver disease but also should recognize the increased risk for CKD and undertake early, aggressive risk factor modifications.

Author contributions

GT researched the data and wrote the manuscript. MC contributed to the discussion and reviewed/edited the manuscript. GZ researched the data and wrote the manuscript. MC contributed to the discussion and reviewed/edited the manuscript. EB contributed to the discussion and reviewed/edited the manuscript.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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