

A brief review on the rising incidence of chronic kidney diseases and non-alcoholic fatty liver disease

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Chronic kidney diseases (CKDs) are the most common forms of kidney disease all around the world. The incidence of CKD is rising, which is mainly driven by population aging as well as by a global rise in hypertension, metabolic syndrome, and metabolic risk factors, particularly obesity and type-2 diabetes. The high mortality, morbidity of CKD, and the health care costs of the renal replacement therapy have led investigators to seek recent and potentially modifiable risk factors such as non-alcoholic fatty liver disease (NAFLD). NAFLD is the hepatic manifestation of metabolic syndrome and the most common cause of chronic liver disease. It incorporates a spectrum of liver diseases ranging from simple steatosis to steatohepatitis, liver cirrhosis, and hepatocellular carcinoma. On the basis of recent publications, the prevalence of CKD is significantly increased among patients with NAFLD, and the prevalence of NAFLD is also higher in CKD patients than in patients without NAFLD. These findings suggest that patients with NAFLD should be screened for CKD and patients with CKD and metabolic syndrome should be screened for NAFLD. Patients with NAFLD and CKD should be treated and followed up by a multidisciplinary team that involves specialists in hepatology, nephrology, diabetes, and cardiology.

Keywords: cardiovascular risk, chronic kidney diseases, epiGFR, metabolic syndrome, non-alcoholic fatty liver disease

Introduction

Kidney disease is a global public health problem affecting >25% of individuals above the age of 65 years in the adult Western population affecting more than 750 million people worldwide (8, 19). Nowadays, chronic kidney diseases (CKDs) are the most common forms of kidney disease, with an estimated prevalence of about 10.4% among men and 11.8% among women all around the world (12). All recently published data seem to indicate that the incidence of CKD is rising (11, 25) and there are international differences in CKD prevalence (3).

The analysis of the data demonstrates that the growing burden of CKD is mainly driven by population aging as well as by a global rise in metabolic syndrome and metabolic risk factors, particularly obesity and type-2 diabetes (11).

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Diagnosis of CKD

CKD is defined by the presence of decreased glomerular filtration rate (eGFR < 60 ml/min/1.73 m²) and/or by evidence of structural and functional abnormalities of the kidneys noted on urine examination (mainly albuminuria/proteinuria), imaging or histology of renal biopsies, which are present for more than 3 months. A five-stage classification system of CKD is devised internationally to guide rating of the severity of CKD cases (14, 15). The five-stage system is based on eGFR (Table I).

GFR is estimated from a single serum creatinine measurement using creatinine-based eGFR equations, from which the CKD epidemiology collaboration (CKD-EPI) equation (epiGFR) is the best accepted at present.

CKD may progress to end-stage renal disease (ESRD). The number of patients requiring renal replacement therapy due to ESRD varies from <30 to >200 persons per million population across European countries, and is much higher in high-income countries (17). Furthermore, the cardiovascular morbidity and mortality of CKD patients is also high.

The major risk factors for the progression of CKD are hypertension, proteinuria, smoking, insulin resistance, and some of the components of metabolic syndrome, such as abdominal obesity, type-2 diabetes mellitus, dyslipidemia, and hyperuricemia. The high mortality and morbidity of CKD and the costs of renal replacement therapies (hemodialysis, peritoneal dialysis, and transplantation) have led investigators to seek potentially modifiable risk factors. A risk factor is a variable that has a causal association with a disease; the presence of the variable in an individual or a population is associated with an increased risk of the presence or future development of a disease (30). One of the recently recognized risk factors is non-alcoholic fatty liver disease (NAFLD) (18).

NAFLD

NAFLD is the hepatic manifestation of metabolic syndrome and the most common cause of chronic liver disease worldwide (10, 18). It is a condition characterized by the accumulation of fat in the liver of people who drink minimal or no alcohol at all and who do not have alternate causes for hepatic steatosis (such as viral infection, drug intoxication, iron overload, or autoimmune disease) (6, 32). NAFLD incorporates a spectrum of liver diseases ranging from simple steatosis to steatohepatitis [non-alcoholic steatohepatitis (NASH)], liver

Table I. Classification of chronic kidney diseases (CKD) by glomerular filtration rate (GFR)

Stage	Description	GFR (ml/min)
1	Kidney damage with normal or elevated GFR	>90
2	Kidney damage with mild decrease of GFR	60–89
3a	Kidney damage with mildly to moderately decreased GFR	45–59
3b	Kidney damage with moderately to severely decreased GFR	30–44
4	Severe decrease of GFR	29–15
5	End-stage renal failure	<15

cirrhosis, and hepatocellular carcinoma (33). The global prevalence of NAFLD is approximately 25%–30% (36). In Europe, the prevalence is between 2% and 44% in the general population (2). The huge variation in the prevalence can be explained by the multitude of methods used for the diagnosis of NAFLD. However, the prevalence is as high as 24%–69.5% in patients with diabetes mellitus (31, 34).

Diagnosis of NAFLD

Laboratory abnormalities

Mildly to moderately elevated levels of serum liver enzymes (aminotransferases and gamma-glutamyltransferase) are the most common and the only laboratory abnormalities frequently found in patients with NAFLD. However, serum liver enzyme levels are not reliable indicators for the diagnosis of NAFLD, as there is no biochemical abnormality in most patients with a spectrum of NAFLD (6).

Imaging

The liver ultrasonography is the recommended first-line examination for the detection of NAFLD in the clinical practice (9). On ultrasound, hepatic steatosis produces a typical diffuse increase in echogenicity (13). The sensitivity and specificity of the method is approximately 85% and 95%, if the fat infiltration of the liver is at least 20%–30%. The method is relatively inexpensive and could help to exclude other causes of liver disease (1, 13).

Histological examination of liver biopsy

The liver biopsy is the standard procedure for diagnosing NASH and for staging the degree of inflammation and fibrosis in patients with more advanced NAFLD (6, 9). However, the method is invasive, potentially risky, and patient unfriendly. For this reason, non-invasive biomarker tests such as NAFLD fibrosis scan and the fibrosis-4 score have been introduced to use them instead of liver biopsy (5).

Relationship Between CKD and NAFLD

CKD in NAFLD

It is now increasingly clear that NAFLD not only affects the liver but can also increase the risk of developing extrahepatic diseases, including cardiovascular diseases and CKD (32). The recent large meta-analysis of Mantovani et al. (18) demonstrated that NAFLD is significantly associated with a 20%–55% increase in the long-term risk of incident CKD (CKD stage ≥ 3) during follow-up of 96,595 adult individuals. However, an important limitation of this meta-analysis is that no studies with liver biopsy-proven NAFLD were available. NAFLD was diagnosed only by biochemistry, fatty liver index, or ultrasonography. Furthermore, in these studies, creatinine-based equations were used to estimate GFR, which do not perform well in patients with liver cirrhosis and obesity. Direct measurement of GFR would give more correct results in these patients. In a previous smaller meta-analysis of partly liver biopsy-proven NAFLD, Musso et al. (21) demonstrated the existence of a higher risk of incident CKD in patients with NASH and advanced fibrosis compared to simple steatosis and non-advanced fibrosis.

NAFLD in CKD

Patients with CKD are known to have high cardiovascular risk. A recent analysis of 1,148 CKD patients showed that the prevalence of NAFLD was 17.9% in this population and NAFLD proved to be a strong independent risk factor for cardiovascular events (7).

Pathophysiological interrelationships between the liver and the kidney

A number of environmental and physiological factors can promote the development of NAFLD. The most common cause of NAFLD is an excessive caloric intake that exceeds caloric expenditure, resulting in a consequential spillover of surplus energy in the form of non-esterified fatty acids from expanded visceral adipose tissue into ectopic fat depots, such as the liver (32).

The amount of hepatic lipids increases in NAFLD, but the most important is the triglyceride accumulation in the liver. Approximately, 60% of hepatic lipid is derived from increased peripheral lipolysis of triglycerides.

The kidney and the liver share a number of pathophysiological pathways that are intrinsically linked to each other (14, 35). NAFLD, especially NASH with or without some degree of liver fibrosis, may promote the elevation of blood pressure, may induce dyslipidemia with atherosclerosis, may exacerbate hepatic insulin resistance through the secretion of different hepatokines (e.g., fibroblast growth factor 21 and fetuin-A), and may release several pro-inflammatory molecules (e.g., tumor necrosis factor- α , C-reactive protein, and interleukin 6), prooxidants (e.g., reactive oxygen species), procoagulant factors (e.g., fibrinogen and plasminogen activator inhibitor-1), and profibrogenic factors (e.g., transforming growth factor- β and connective tissue growth factor). These factors and molecules may play an important role in the pathophysiology of CKD and other vascular complications (20, 22, 24, 32).

Other risk factors for NAFLD also have the potential to influence the development of CKD. Increased intake of dietary fructose, decreased vitamin D₃ level, abdominal adiposity, and insulin resistance can also promote the development of NAFLD and contribute to the development of CKD (16). Dietary fructose (particularly, the glucose–fructose syrup in sugar drinks) has become a major public health issue, because it not only increases the hepatic *de novo* lipogenesis contributing to the development of NAFLD, but also increases the level of serum uric acid (27, 28). The increased urinary excretion of uric acid in patients with hyperuricemia can damage the kidney causing CKD in some of the patients (28).

The gut microbiota may be significantly altered in patients with CKD along with impaired intestinal barrier function. These alterations allow translocation of various gut-derived products into the systemic circulation, contributing to the development and progressions of CKD (29). In obese and type-2 diabetic patients, the intestinal dysbiosis is common and can also potentially influence NAFLD and CKD through multiple and complex mechanisms (4, 23, 26).

Conclusions

The liver and kidney share a number of pathophysiological pathways that are intrinsically linked to each other. NAFLD is the most frequent chronic liver disease in the Western society and its prevalence is likely to rise even further. It is not only a potentially progressive liver disease but also has systemic consequences. For example, the prevalence of CKD is significantly increased among patients with NAFLD. On the basis of a recent examination, the prevalence of NAFLD is higher in advanced CKD patients than in patients without CKD.

On the whole, these findings suggest that patients with NAFLD should be screened for CKD with CKD-EPI GFR and with urine examination for proteinuria/albuminuria. Similarly, patients with CKD and metabolic syndrome should be screened for NAFLD with liver enzymes and hepatic ultrasonography. At present, there is no accepted treatment for NAFLD, but lifestyle changes (e.g., weight loss with diet and increased physical activity), nephro-protective diet, drug dosage adjustment to kidney function, and early aggressive treatment of all the existing cardiovascular risk factors may help to prevent or slow down the development and/or progression of CKD in NAFLD patients. Targher and Byrne (32) suggest that patients with NAFLD and CKD should be treated and followed up by a multidisciplinary team that includes specialists in hepatology, nephrology, diabetes, and cardiology.

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