Physiology International, Volume 106 (4), pp. 305–310 (2019)
DOI: 10.1556/2060.106.2019.35

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

J Nagy*, T Kovács*

2nd Department of Internal Medicine, Nephrological and Diabetological Centre, Clinical Centre, Medical School, University of Pécs, Pécs, Hungary

Received: October 6, 2019
Accepted: November 11, 2019

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).

*Both authors contributed equally to this work.
Corresponding author: Dr. Judit Nagy, MD, PhD, DSc
2nd Department of Internal Medicine, Nephrological and Diabetological Centre, Clinical Centre, Medical School, University of Pécs
Pacsirta Street 1, Pécs 7624, Hungary
Phone: +36 72 530 000 36074; Fax: +36 72 536 073; E-mail: judit.nagy@aok.pte.hu

Diagnosis of CKD

CKD is defined by the presence of decreased glomerular filtration rate (eGFR < 60 ml/min/1.73 m^2) 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 D_3 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), nephroprotective 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.

REFERENCES

1. Ballestri S, Nascimbeni F, Baldelli E, Marrazzo A, Romagnoli D, Targher G, Lonardo A: Ultrasonographic fatty liver indicator detects mild steatosis and correlates with metabolic/histological parameters in various liver diseases. Metabolism 72, 57–65 (2017)
2. Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F: The burden of liver disease in Europe: a review of available epidemiological data. J. Hepatol. 58, 593–608 (2013)
3. Brück K, Stel VS, Gambaro G, Hallan S, Völzke H, Ärnlöv J, Kastarinen M, Guessous I, Vinhas J, Stengel B, Brenner H, Chudek J, Romundstad S, Tomson C, Gonzalez AO, Bello AK, Ferrieres J, Palmieri L, Browne G, Capuano V, Van Biesen W, Zoccali C, Gansevoort R, Navis G, Rothenbacher D, Ferraro PM, Nitsch D, Wanner C, Jager KJ; European CKD Burden Consortium: CKD prevalence varies across the European general population. J. Am. Soc. Nephrol. 27, 2135–2147 (2016)
4. Boursier J, Mueller O, Barret M, Machado M, Fizanne L, Araujo-Perez F, Guy CD, Seed PC, Rawls JF, David LA, Hunault G, Oberti F, Calès P, Diehl AM: The severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota. Hepatology 63, 764–775 (2016)
5. Castera L, Vilgrain V, Angulo P: Noninvasive evaluation of NAFLD. Nat. Rev. Gastroenterol. Hepatol. 10, 666–675 (2013)
6. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ: The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology 55, 2005–2023 (2012)
7. Chinnadurai R, Ritchie J, Green D, Kalra PA: Non-alcoholic fatty liver disease and clinical outcomes in chronic kidney disease. Nephrol. Dial. Transpl. 34, 449–457 (2019)
8. Crews DC, Bello AK, Saadi G, World Kidney Day Steering Committee: Burden, access, and disparities in kidney disease. Kidney Int. 95, 242–248 (2019)
9. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. J. Hepatol. 64, 1388–1402 (2016)
10. Fazel Y, Koenig AB, Sayiner M, Goodman ZD, Younossi ZM: Epidemiology and natural history of non-alcoholic fatty liver disease. Metabolism 65, 1017–1025 (2016)
11. Fraser SDS, Roderick PJ: Kidney disease in the Global Burden of Disease Study 2017. Nat. Rev. Nephrol. 15, 193–194 (2019)
12. GBD 2013 Mortality and Causes of Death Collaborators: Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 385, 117–171 (2015)
13. Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, Clark JM: Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology 54, 1082–1090 (2011)
14. James MT, Hemmelgarn BR, Tonelli M: Early recognition and prevention of chronic kidney disease. Lancet 375, 1296–1309 (2010)
15. Kiapidou S, Liava C, Kalogirou M, Akriviadis E, Sinakos E: Chronic kidney disease in patients with non-alcoholic fatty liver disease: what the hepatologist should know? Ann. Hepatol. (2019) [Epub ahead of print]

16. Kovesdy CP, Furth S, Zoccali C, World Kidney Day Steering Committee: Obesity and kidney disease: hidden consequences of the epidemic. Physiol. Int. 104, 1–14 (2017)
17. Kramer A, Pippias M, Stel VS, Bonthuis M, Abad Diez JM, Afentakis N, Alonso de la Torre R, Ambuhl P, Bikbov B, Bouzas Caamaño E, Bubic I, Buturovic-Ponikvar J, Caskey FJ, Castro de la Nuez P, Cernevskis H, Collart F, Comas Farnés J, Garcia Bazaga Mde L, De Meester J, Ferrer Alamar M, Finne P, Garneata L, Golan E, G Heaf J, Hemmelder M, Ioannou K, Kantaria N, Kolesnyk M, Kramar R, Lassalle M, Lezaic V, Lopot F, Macário F, Magaz A, Martín-Escobar E, Metcalfe W, Ots-Rosenberg M, Palsson R, Piñera Celestino C, Resić H, Rutkowski B, Santiuste de Pablos C, Spustová V, Stendahl M, Strakosha A, Süleymanlar G, Torres Guinea M, Varberg Reisæter A, Vazelov E, Ziginskiene E, Massy ZA, Wanner C, Jager KJ, Noordzij M: Renal replacement therapy in Europe: a summary of the 2013 ERA-EDTA Registry Annual Report with a focus on diabetes mellitus. Clin. Kidney J. 9, 457–469 (2016)
18. Mantovani A, Zaza G, Byrne CD, Lonardo A, Zoppini G, Bonora E, Targher G: Nonalcoholic fatty liver disease increases risk of incident chronic kidney disease: a systematic review and meta-analysis. Metabolism 79, 64–76 (2018)
19. McCullough K, Sharma P, Ali T, Khan I, Smith WC, MacLeod A, Black C: Measuring the population burden of chronic kidney disease: a systematic literature review of the estimated prevalence of impaired kidney function. Nephrol. Dial. Transplant. 27, 1812–1821 (2012)
20. Meex RCR, Watt MJ: Hepatokines: linking nonalcoholic fatty liver disease and insulin resistance. Nat. Rev. Endocrinol. 13, 509–520 (2017)
21. Musso G, Gambino R, Tabibian JH, Ekstedt M, Kechagias S, Hamaguchi M, Hultcrantz R, Hagström H, Yoon SK, Charatcharoenwitthaya P, George J, Barrera F, Hafliðadóttir S, Björnsson ES, Armstrong MJ, Hopkins LJ, Gao X, Francque S, Verrijken A, Yilmaz Y, Lindor KD, Charlton M, Haring R, Lerch MM, Rettig R, Völzke H, Ryu S, Li G, Wong LL, Machado M, Cortez-Pinto H, Yasui K, Cassader M: Association of non-alcoholic fatty liver disease with chronic kidney disease: a systematic review and meta-analysis. PLoS Med. 11, e1001680 (2014)
22. Musso G, Cassader M, Cohney S, De Michieli F, Pinach S, Saba F, Gambino R: Fatty liver and chronic kidney disease: novel mechanistic insights and therapeutic opportunities. Diabetes Care 39, 1830–1845 (2016)
23. Nallu A, Sharma S, Ramezani A, Muralidharan J, Raj D: Gut microbiome in chronic kidney disease: challenges and opportunities. Transl. Res. 179, 24–37 (2017)
24. Petersen MC, Shulman GI: Roles of diacylglycerols and ceramides in hepatic insulin resistance. Trends Pharmacol. Sci. 38, 649–665 (2017)
25. Said A, Desai C, Lerma EV: Chronic kidney disease. Dis. Mon. 61, 374–377 (2015)
26. Sampaio-Maia B, Simoes-Silva L, Pestana M, Araujo R, Soares-Silva IJ: The role of the gut microbiome on chronic kidney disease. Adv. Appl. Microbiol. 96, 65–94 (2016)
27. Scorletti E, Calder PC, Byrne CD: Non-alcoholic fatty liver disease and cardiovascular risk: metabolic aspects and novel treatments. Endocrine 40, 332–343 (2011)
28. Softic S, Cohen DE, Kahn CR: Role of dietary fructose and hepatic de novo lipogenesis in fatty liver disease. Dig. Dis. Sci. 61, 1282–1293 (2016)
29. Sumida K, Kovesdy CP. The gut-kidney-heart axis in chronic kidney disease. Physiol. Int. 106, 195–206 (2019)
30. Taal MW (2012): Risk factors and chronic kidney disease. In: Brenner & Rector's The Kidney, eds Taal MW, Chertow GM, Marsden PA, Skorecki K, Yu ASL, Brenner BM, Elsevier, Philadelphia, pp. 758–777
31. Targher G, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, Day C, Arcaro G: Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care 30, 1212–1218 (2007)
32. Targher G, Byrne CD: Non-alcoholic fatty liver disease: an emerging driving force in chronic kidney disease. Nat. Rev. Nephrol. 13, 297–310 (2017)
33. Vernon G, Baranova A, Younossi ZM: Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment. Pharmacol. Ther. 34, 274–285 (2011)
34. Williamson RM, Price JF, Glancy S, Perry E, Nee LD, Hayes PC, Frier BM, Van Look LA, Johnston GI, Reynolds RM, Strachan MW: Prevalence of and risk factors for hepatic steatosis and nonalcoholic fatty liver disease in people with type 2 diabetes: the Edinburgh type 2 diabetes study. Diabetes Care 34, 1139–1144 (2011)
35. Wong VW, Wong GL, Choi PC, Chan AW, Li MK, Chan HY, Chim AM, Yu J, Sung JJ, Chan HL: Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years. Gut 59, 969–974 (2010)
36. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M: Global epidemiology of nonalcoholic fatty liver disease – meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 64, 73–84 (2016)