Received: 1 January 2022 | Accepted: 16 January 2022

DOI: 10.1111/eci.13748

REVIEW

WILEY

Fatty kidney: A possible future for chronic kidney disease research

Mehmet Kanbay[1] | **Sidar Copur**[2] | **Atalay Demiray**[2] | **Alan A. Sag**[3] | **Adrian Covic**[4] | **Alberto Ortiz**[5] | **Kathherine R. Tuttle**[6,7]

[1]Division of Nephrology, Department of Medicine, Koc University School of Medicine, Istanbul, Turkey

[2]Department of Medicine, Koc University School of Medicine, Istanbul, Turkey

[3]Division of Vascular and Interventional Radiology, Department of Radiology, Duke University Medical Center, Durham, North Carolina, USA

[4]Department of Nephrology, Grigore T. Popa' University of Medicine, Iasi, Romania

[5]Department of Medicine, Universidad Autonoma de Madrid and IIS-Fundacion Jimenez Diaz, Madrid, Spain

[6]Division of Nephrology, University of Washington, Seattle, Washington, USA

[7]Providence Medical Research Center, Providence Health Care, Spokane, Washington, USA

Correspondence
Mehmet Kanbay, Koc University School of Medicine, Istanbul 34010, Turkey.
Email: mkanbay@ku.edu.tr

Abstract

Background: Metabolic syndrome is a growing twenty-first century pandemic associated with multiple clinical comorbidities ranging from cardiovascular diseases, non-alcoholic fatty liver disease and polycystic ovary syndrome to kidney dysfunction. A novel area of research investigates the concept of fatty kidney in the pathogenesis of chronic kidney disease, especially in patients with diabetes mellitus or metabolic syndrome.

Aim: To review the most updated literature on fatty kidney and provide future research, diagnostic and therapeutic perspectives on a disease increasingly affecting the contemporary world.

Materials and Method: We performed an extensive literature search through three databases including Embase (Elsevier) and the Cochrane Central Register of Controlled Trials (Wiley) and PubMed/Medline Web of Science in November 2021 by using the following terms and their combinations: 'fatty kidney', 'ectopic fat', 'chronic kidney disease', 'cardiovascular event', 'cardio-metabolic risk', 'albuminuria' and 'metabolic syndrome'. Each study has been individually assessed by the authors.

Results: Oxidative stress and inflammation, Klotho deficiency, endoplasmic reticulum stress, mitochondrial dysfunction and disruption of cellular energy balance appear to be the main pathophysiological mechanisms leading to tissue damage following fat accumulation. Despite the lack of large-scale comprehensive studies in this novel field of research, current clinical trials demonstrate fatty kidney as an independent risk factor for the development of chronic kidney disease and cardiovascular events.

Conclusion: The requirement for future studies investigating the pathophysiology, clinical outcomes and therapeutics of fatty kidney is clear.

KEYWORDS

chronic kidney disease, diabetes mellitus, fatty kidney, metabolic syndrome, novel therapy

1 | INTRODUCTION

Metabolic syndrome, a growing pandemic leading to significant morbidity and mortality, is characterized by high blood pressure, hypertriglyceridemia, high fasting blood glucose levels and abdominal obesity characterized by waist circumference over 88 cm in females and 102 cm in males.[1,2] According to estimations by the International Diabetes Federation (IDF) and the National Cholesterol Education Program, the prevalence of metabolic syndrome is around 30% in the US adult population.[3] Patients with metabolic syndrome are more likely to develop non-alcoholic fatty liver disease (NAFLD), atherosclerosis, coronary artery disease, peripheral artery disease, certain malignancies and kidney dysfunction.[1,4] A novel approach referred as global cardiometabolic risk (CMR), which includes additional criteria such as age, smoking status, family history and gender, has been developed since criteria used to define metabolic syndrome are poor indicator of global cardiovascular disease (CVD) risk.[5,6] In this approach, the presence of metabolic syndrome is only another criterion for the development of CVD rather than being a direct indicator. Accumulation of adipose tissue in various tissues including liver, kidney, pancreas and heart is commonly encountered in overweight or obese patients and imposes increased risk for CVD. Such association is linked to dysregulation of adipokines and pro- or anti-inflammatory cytokines in addition the key pathophysiological contributor, insulin resistance.[6,7]

Fatty kidney is defined as abnormally increased fat volume in the renal interstitium (encasing renal vascular, lymphatic, urinary collecting system and nervous structures).[8,9] Although a higher prevalence of chronic kidney disease has been reported among patients with metabolic syndrome, the relationship between these two entities appears to be bidirectional rather than causal.[10–12] Insulin resistance is the most important link between chronic kidney disease and metabolic syndrome, as insulin resistance is linked to inflammation, oxidative stress, fibrosis, mesangial cell proliferation and expansion, podocyte hypertrophy, glomerular basement membrane thickening, arterial hyalinosis, intimal thickening and adipose tissue accumulation.[13,14]

This report aims to review the most updated literature on this topic and provide future research, diagnostic and therapeutic perspectives on a disease increasingly affecting the contemporary world.

2 | LITERATURE SEARCH STRATEGY

We performed an extensive literature search through three databases including Embase (Elsevier) and the Cochrane Central Register of Controlled Trials (Wiley) and PubMed/Medline Web of Science in November 2021 by using the following terms and their combinations: 'fatty kidney', 'ectopic fat', 'chronic kidney disease', 'cardiovascular event', 'cardio-metabolic risk', 'albuminuria' and 'metabolic syndrome'. Each study has been individually assessed by the authors. Reference lists of each study have been evaluated manually in order not to miss any relevant study. After preliminary elimination of the studies with evaluation of the titles and abstracts, full-text studies are evaluated by the authors independently. All clinical trials including prospective or retrospective cohort studies, case–control studies and cross-sectional studies investigating the effects of ectopic fat accumulation in renal tissue on renal or cardiovascular consequences and published in a peer-reviewed journal in English until November 2021 have been included in this narrative review. Additionally, studies investigating the pathophysiology underlying the ectopic fat accumulation in renal tissue have been reviewed.

3 | LIPID METABOLISM IN THE KIDNEYS

Hypertriglyceridemia and hypercholesterolemia predispose to developing lipid deposits in most cell types of the kidneys including tubular epithelium, podocytes and mesangial cells as shown in mouse and rat models of metabolic syndrome and diabetes, as well as in human biopsy specimens.[15–19] Although studies in humans are limited in number and extent, there is a growing preclinical literature on the subject via studies performed in rodent models and potentially shared mechanisms with NAFLD. CD36, along with soluble lipid carriers (SLC27A1-6), is the main cellular transporter of lipids, predominantly oxidized low-density lipoprotein cholesterol (LDL-C). CD36 is found on almost all types of renal cells.[20–24] CD36 knockout mice are less likely to develop fatty kidney and chronic kidney disease in response to hyperlipidaemia and hypertriglyceridemia, but no studies have been performed in human subjects.[25,26] However, Mendelian randomization studies would be possible, given that several loss of function genetic variants are found at a frequency of around 1 in 1000.[27] The role of CD36 in lipid transport has been demonstrated in other cell types including hepatocytes, endothelial cells and malignant cells.[20,23,28] Metabolites of oxidized LDL-C, namely 9-hydroxyoctadecanoic acid and 13-octadecenoic acid, activate transcription factors involved in adipogenesis including the peroxisome proliferator-activated receptor γ (PPARγ) and exert a positive feedback on CD36 expression.[29] Binding of fatty acids to CD36 induces upregulation of CD36 and translocation of CD36 from cytoplasm to plasma membrane and thus over-uptake of lipids into renal cells.[20,29] Binding of fatty

acids or LDL-C to CD36 leads to apoptosis of podocytes and renal tubular epithelial cells via formation of reactive oxygen species and production of thrombospondin-1.[30–32] An alternative theoretical mechanism for renal fat accumulation is the differentiation of multipotent mesenchymal progenitor cells; however, no studies have yet demonstrated such differentiation (Figure 1).

3.1 | Cholesterol

The primary functional role of cholesterol in podocytes is the proper localization and function of the slit diaphragm in the filtration barrier.[33] Although the main factor contributing to excess cholesterol accumulation is the defective efflux of cholesterol from podocytes, serum cholesterol levels also contribute, as inferred by the beneficial effects of statin administration which in turn activates the phosphatidylinositol 3-kinase/AKT-signalling pathway.[34,35] Of note, statins have not been shown to impact kidney function positively or negatively in clinical trials.[34–36] In contrast, depletion of cholesterol via cyclodextrin (which sequesters cholesterol) restores podocyte function and prevents podocyte apoptosis in mice with Niemann-Pick type C1, a disease caused by mutation in the NPC1 gene and characterized by lysosomal cholesterol accumulation in cells of various tissues, including liver and kidney.[37] NPC1 is a membrane receptor that allows intracellular trafficking of cholesterol and cholesterol exit from lysosomes. LDL-C is uptaken into podocytes via the LDL-C receptor CXCL16, and high intracellular levels of LDL-C along with triglycerides and free fatty acids (FFA) may cause oxidative and endoplasmic reticulum (ER) stress.[38]

3.2 | Free fatty acids

Accumulation of FFA is mediated via uptake through CD36, especially if associated with decreased fatty acid beta oxidation. The majority of FFA accumulates in lipid droplets or in the mitochondrial matrix, leading to formation of reactive oxygen species and lipid peroxidation.[39,40] Moreover, LDL-C receptor regulation is disrupted in pre-diabetic and diabetic patients, which may be due to induction of an enzyme involved in desaturation of free fatty acids, stearoyl-CoA desaturase 1 and decreased expression of ATP-binding cassette transporter (ABCA1).[41,42]

3.3 | Genetic abnormalities

Mutations in the gene encoding APOL1, a particle localized in high-density lipoprotein (HDL-C) and involved in the efflux of cholesterol, which is a principal mechanism of cholesterol accumulation in podocytes and renal tissue, or ABCA1, which is involved in the efflux of cholesterol, are associated with increased risk for chronic kidney disease if two mutated alleles are present.[33,43–46] APOL1 is also expressed in podocytes and vascular cells and risk variants of APOL1 protect from trypanosomiasis but are associated with chronic kidney disease in African American in response to diverse triggers, including HIV or SARS-CoV-2 infection.[47,48] Over-expression of APOE and deficiency of lecithin-cholesterol acyltransferase (LCAT) (involved in the esterification of free cholesterol in plasma or APOA1) is linked to nephrotic-range proteinuria and focal segmental glomerulosclerosis.[49–52]

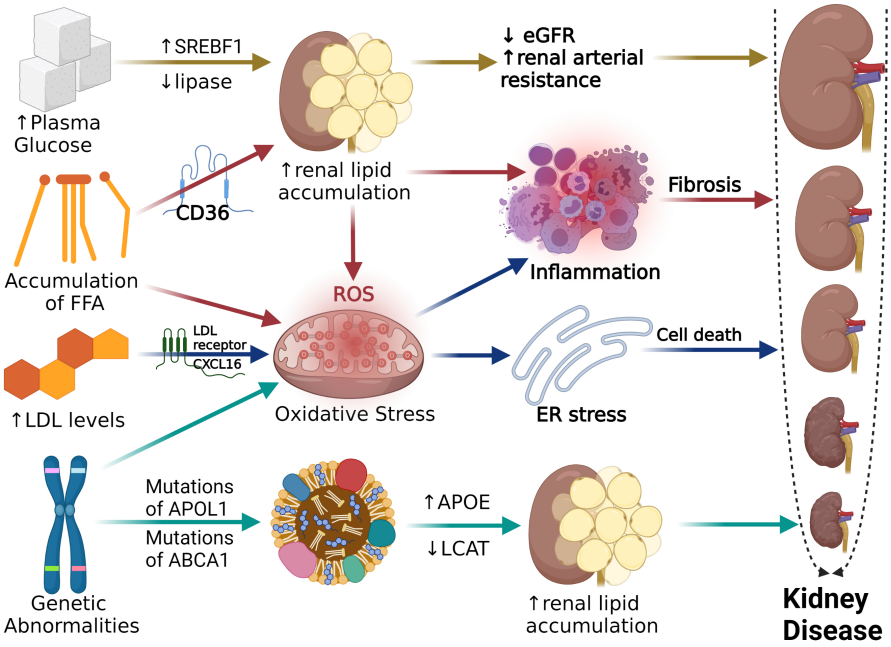

FIGURE 1 Potential mechanisms leading to renal fat accumulation and kidney disease. ABCA1, ATP-binding cassette transporter A1; APOE, Apolipoprotein E; APOL1, gene encoding apolipoprotein L1; eGFR, estimated glomerular filtration rate; ER, endoplasmic reticulum; FFA, free fatty acid; LCAT, lecithin:cholesterol acyltransferase; LDL, low-density lipoprotein; ROS, reactive oxygen species; SREBF1, sterol regulatory element binding transcription factor 1

3.4 | Glucose

High plasma glucose levels lead to increased renal lipid accumulation through alteration of transcription factors such as the over-expression of sterol regulatory element-binding transcription factor 1 (SREBF1) and suppression of adipocyte triglyceride lipase, among others.[53–55] In patients with type 2 diabetes mellitus, pararenal and perirenal adipose tissue thickness is an independent risk factor for low estimated glomerular filtration rate (eGFR) and increased renal arterial resistance.[56,57] Chronic hyperglycaemia leads to lipogenesis and disrupts the FFA entry into the mitochondrial citric acid cycle (Krebs cycle), thus inhibiting the lipolysis.

4 | PATHOGENESIS OF KIDNEY INJURY IN FATTY KIDNEY

Perirenal adipose tissue is the retroperitoneal fat that surrounds the kidneys.[58] The renal sinus fat is considered part of the perirenal adipose tissue even though it is technically inside the kidney. High-serum total cholesterol, high very low-density lipoprotein cholesterol (VLDL-C), high LDL-C, high fasting plasma glucose or HbA1c, high gamma-glutamyl transferase and low HDL-C levels are the major variables that associate with greater renal sinus fat accumulation along with certain medical conditions including hypertension, diabetes mellitus and metabolic syndrome (Figure 2).[8,59]

There are two hypotheses regarding how fat accumulation in the kidneys may cause kidney disease. The first, based on work by Moorhead and colleagues, assumes that renal parenchymal fat accumulation leads to inflammation and oxidative stress with pro-inflammatory cytokines that damage the renal vasculature, mesangial cells, proximal tubule epithelium and podocytes, thus creating a local environment of electrical insulation, possibly impairing cross-talk between the kidney and other organs.[60] The second hypothesis is that renal sinus fat accumulation in a confined space leads to compression of the renal vasculature, or even a compressive depolarization of the nerves lining the vessels, thereby activating the renin–angiotensin–aldosterone system.[61,62]

4.1 | Inflammation and oxidative stress

Accumulation of lipids including VLDL-C, LDL-C, FFAs and cholesterol crystals in nephrons, especially proximal tubular epithelium and podocytes, plays a crucial role in the pathogenesis of fatty kidney. Such molecules are prone to various degrees of oxidation with formation of lipid peroxides that promote the release of pro-inflammatory cytokines including IL-1, IL-6, IL-8 and TNF-alpha from monocytes, macrophages and mesangial cells.[8,63,64] Even in the absence of lipid peroxidation, renal sinus fat may be a source of adipokines, leptin, chemokines and cytokines comparable to adipose tissue elsewhere.[63,65,66] Disruption of the balance between pro-inflammatory and anti-inflammatory cytokines in the renal tissue leads to accumulation of inflammatory cells, tissue damage, cell death, formation of reactive oxygen species and defective energy homeostasis, all of which contribute to further progression of CKD. Regardless of aetiology, the result is post-inflammatory fibrosis, histologically characterized by defective fatty acid oxidation in renal tissue or hyperlipidaemia. Defective fatty acid oxidation may be attributable to inhibition of AMP-activated protein kinase (AMPK), PPAR-alpha or PPAR-gamma pathways, disrupted mitochondrial function due to enzyme or cofactor deficiency or mitochondrial damage and defective cellular trafficking of lipids.[67–69]

4.2 | Mitochondrial dysfunction

The mitochondria metabolize key molecules in this domain, including beta oxidation of fatty acids, urea cycle, synthesis of porphyria and performance of the Krebs cycle.[70] After being transported into cells, free fatty acids undergo an acylation process, in which coenzyme is linked to the fatty acid structure followed by transport into the mitochondrial matrix via carnitine palmitoyltransferase 1 and 2 enzymes.[71] Accumulation of fatty acids in the mitochondria of renal tubular cells, especially proximal tubular cells, is a common pathological finding in either ischaemic, toxic or septic renal injuries due to disruption between lipolysis-to-lipogenesis ratio.[72,73] Accumulation of non-esterified fatty acids has been hypothesized to be a major contributor of mitochondrial dysfunction.[74–76] Accumulation of such molecules in mitochondrial matrices inhibits essential functions of mitochondria, which may further worsen cellular injury.

4.3 | Klotho deficiency

Klotho is a protein produced mainly by the kidney, which has anti-ageing, anti-inflammatory, antioxidant and anti-fibrotic properties.[77] Acute and chronic kidney disease are conditions of acquired Klotho deficiency associated with accelerated tissue ageing, as is the case for genetic Klotho deficiency. Hyperlipidaemia-associated renal damage was characterized by decreased kidney Klotho in ApoE knockout mice.[78] The antioxidant properties of Klotho are evident in a uremic milieu.[79]

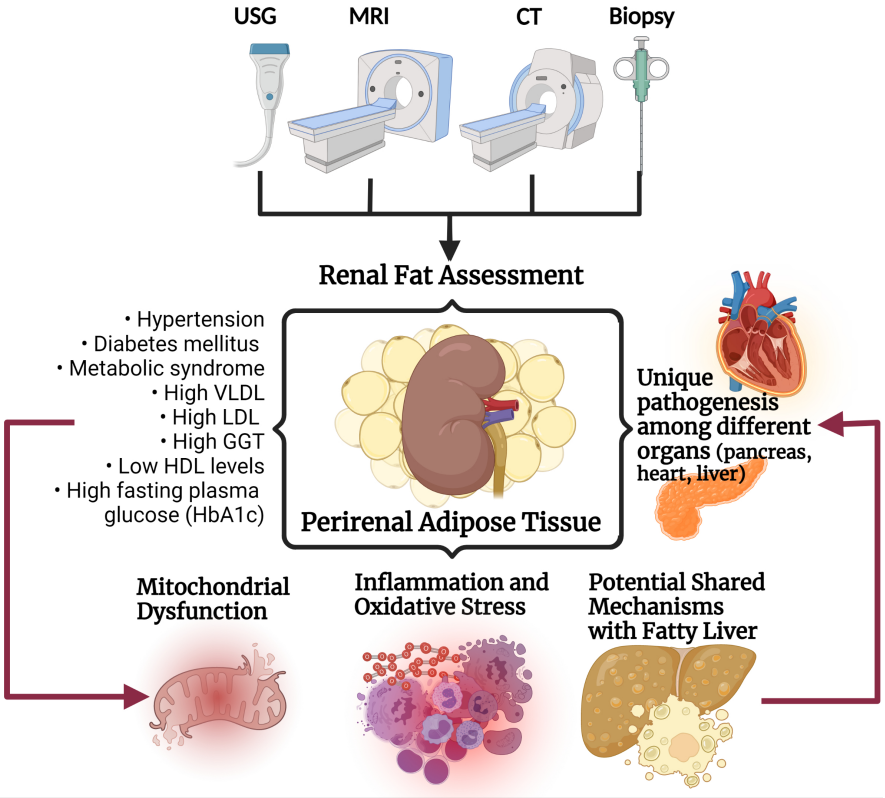

FIGURE 2 Overview of perirenal adipose tissue including its associated factors, assessment and possible contribution to pathogenesis. CT, computed Tomography; GGT, Gamma-glutamyl transferase; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; USG, ultrasonography; VLDL, very low-density lipoproteins

4.4 | Other potential shared mechanisms with fatty liver

Other pathophysiological mechanisms have been described for NAFLD that may be relevant for fatty kidneys, such as ER stress, mainly referring to the unfolded protein response, mediated by accumulation of palmitic acid, may lead to protein degradation, disruption of protein synthesis and JNK-mediated apoptosis.[4,80,81] Two major hormones secreted by the adipose tissue, namely leptin, which inhibits food intake and induces energy expenditure and adiponectin which increases insulin sensitivity, play crucial roles in fatty liver pathophysiology, in which low serum levels of adiponectin and significant resistance to leptin along with high-serum leptin concentration have been documented.[82–86] An altered gut microbiome also influences both liver and kidney function and injury.[87–90]

Certain genetic variations have been linked to both NAFLD and fatty kidney among which the patatin-like phospholipase domain-containing protein-3 (PNPLA3) I148 M gene variant constitutes the greater proportion of genetic variability among patients with NAFLD along with the incidence of CKD assessed via decline in eGFR, fatty kidney and albuminuria in children and adults.[91-97] Although exact mechanism underlying the role of PNPLA3 gene polymorphism on NAFLD and fatty kidney has not been fully understood, it is mainly expressed in hepatic stellate cells and renal podocytes and leads to inflammation and fibrosis in response to fat droplet formation. Major importance of this genetic polymorphism in addition to its' high prevalence in that population is the potential treatability with retinoic acid receptor agonists.[98]

5 | FATTY KIDNEY AND KIDNEY AND CARDIOVASCULAR DISEASE

The Framingham Heart Study reported a high incidence of imaging consistent with fatty kidney, 30%, which is assessed via 8-slice Multi-Detector CT imaging.[99] This and other studies have shown an association between fatty kidneys and kidney and cardiovascular outcomes. In 2923 subjects from the Framingham Heart Study, fatty kidney was associated with the incidence of hypertension and chronic kidney disease after adjustment for body mass index and gender.[99] One major limitation of this study is the utilization of cystatin C for chronic kidney disease and eGFR evaluation, which may itself be increased by obesity. Therefore, results of the Framingham Heart Study in terms of the association between fatty kidney and chronic kidney disease may be misleading since a similar relationship has not been documented when creatinine has been used as the marker for eGFR evaluation. In fifty-one patients with type 2 diabetes, renal sinus fat was negatively correlated with GFR and effective renal plasma flow and positively correlated with effective renal vascular resistance

and mean arterial pressure mellitus after adjustments for body mass index, visceral adipose tissue and gender.[100] Perirenal adipose tissue has been linked to carotid intima–media thickness, vascular calcifications, visceral adiposity, hypertension and number of medications used in the treatment of hypertension, atherosclerosis, cardiovascular events, microalbuminuria and progression of chronic kidney disease in multiple large-scale studies.[63,101–107] Although most studies, especially the cross-sectional studies, do not consider perirenal fat thickness or renal sinus fat as an individual risk factor for the development of CKD, a few studies demonstrate that both are individual risk factors independent from other traditional risk factors. General characteristics of the major studies investigating such relationships have been reviewed at Table 1.

Another important issue to be addressed is the potential effects of fat accumulation in other tissues including epicardium on cardio-renal outcomes. Epicardial fat accumulation has been linked to poor consequences including albuminuria, decline in eGFR, atherosclerosis and worse prognosis in CKD patients.[108–111] Exact physiological role of epicardial fat accumulation is currently unclear; nevertheless, it is involved in the secretion of many cytokines such as leptin, adiponectin, resistin, omentin and others. Under physiological conditions, the balance of these cytokines supports anti-inflammatory and anti-atherogenic effects while excess accumulation of epicardial fat accumulation leads to contradictory outcomes like fat accumulation in many other tissues including liver, kidney and subcutaneous tissues.[112,113] Additionally, epicardial fat accumulation supports myocardial tissue, which primarily utilizes free fatty acids as energy source. Although studies investigating the cardio-renal effects of fatty accumulation in other tissues are scarce, similar pathophysiological effects are possible.

6 | IMAGING OF FATTY KIDNEY

Ultrasound is a noninvasive, inexpensive modality that is widely available. Unfortunately, the detection of fat is a major limitation of ultrasound imaging and image quality, as fat disrupts the sound waves and reduces image quality.[114,115] Therefore, evaluation of a deep organ in overweight individuals can be challenging and require technical skill. Nevertheless, ultrasound delivers no ionizing radiation and provides real-time point of care analysis; therefore, it is worth considering this option. This assessment will usually implement lower-frequency curved transducers, which are suited for deep penetration.

One objective imaging biomarker is the thickness of the abdominal subcutaneous fat layer (defined as the distance between the dermis and abdominal musculature) and thickness of the visceral fat (defined as the distance from the peritoneum to the transverse process of the lumbar spine). Of note, since fat is compressible, these measurements are fraught with random and systematic error based on how heavily the operator presses on the patient's tissue and fat thickness differences of 1–2 cm in the subcutaneous fat layer can be created simply by pressing too hard on the skin to achieve a more optimal image quality.[116] Despite being used in multiple studies, ultrasound has not yet been recommended in the assessment of renal sinus or parenchymal fat content.[117,118] One of the reasons may be that the kidney is inconsistently visualized by ultrasound, especially in overweight individuals, due to such variables as bowel gas and visceral adiposity limiting image quality.

CT uses ionizing radiation to create cross-sectional images of the abdomen and provides reproducible, objective imaging of the abdominal subcutaneous and visceral fat layers with high sensitivity and specificity.[116] However, it delivers a radiation dose to the patient that limits its value as a screening modality. Intravenous contrast is not needed to assess fat content and actually non-contrast assessment may be preferred as it allows accurate measurement of the native tissue density (measured in Hounsfield units), which will be in the negative range for fatty tissue. However, exact delineation of intrarenal fat content is difficult without contrast since the papillae, collecting system, vessels and sinus fat all have similar densities, are crowded and often not best seen in the routine axial/sagittal/coronal planes. Addition of contrast (especially in the context of patients at risk of contrast induced nephropathy) is unlikely to help substantially, but if performed, would be most useful with a split phase contrast technique: in the nephrographic phase, the enhancing tissue (nephrons, vessels, collecting system) can all be volumetrically subtracted from the non-enhancing tissue (presumed to be fat and interstitial tissue, though the measurement of these densities can be inaccurate as the enhancing tissue would make the fat pixels measure brighter on average). In addition, perirenal fat thickness measured manually via CT is better correlated with the perirenal adipose area than the adipose area of the renal sinus.[119]

The best modality to measure fat in a crowded organ like the kidney is magnetic resonance imaging (MRI).[120–122] MRI images protons that are in a fat environment and can be selected and enhanced accurately, and even selectively deactivated (fat saturation sequences). MRI and proton magnetic resonance spectroscopy have been used to assess renal fat content in various studies in addition to

TABLE 1 General characteristics of the clinical studies investigating the effects of fatty kidney

Study	Type of study	Characteristics of the study group	Characteristics of the control group	Method of PF assessment	Outcomes
Foster et al. (2011)	Prospective cohort study	*N* = 879 Age = 61 Gender = 42.7% Female Renal sinus fat = 0.97 BMI = 30.3 eGFR = 84.0 UACR = 5.4	N = 2044 Age = 51 Gender = 54.6% Female Renal sinus fat = 0.18 BMI = 26.6 eGFR = 90.9 UACR = 4.5	Abdominal MDCT scan	Renal sinus fat Systolic and diastolic BP Serum creatinine and cystatin C Urinary albumin and creatinine Fasting plasma glucose and lipids Waist circumference and BMI
Chughtai et al. (2010)	Prospective cohort study	*N* = 205 Age = 69 Gender = 49% Female BMI = 30 Renal sinus fat = 4.2 cm3 SC fat = 195 cm3 RP fat = 55 cm3 IP fat = 129 cm3	N/A	MRI	Renal sinus fat Systolic and diastolic BP Serum creatinine, electrolytes, glucose, lipids, CRP
Bassols et al. (2018)	Cross-sectional study	*N* = 702 Age = 8.3 Gender = 46.7% Female BMI = 19.8 cIMT = 0.04 cm SC fat = 0.96 cm IA fat = 5.9 cm Perirenal fat = 0.21 cm	N/A	USG	Carotid intima–media thickness Perirenal fat thickness Systolic and diastolic BP BMI and body composition analysis Preperitoneal, intra-abdominal and subcutaneous fat thickness Serum glucose, lipids and insulin
Manno et al. (2019)	Prospective cohort study	*N* = 102 Age = 42.3 BMI = 33.4 Perirenal fat = 25.4 mm Epicardial fat = 5.65 cm	N/A	USG and ECHO	Para and perirenal fat thickness Epicardial fat thickness Serum glucose, lipids and insulin levels BMI and waist circumference
Geraci et al. (2018)	Cross-sectional study	*N* = 296 Age = 61 Gender = 32.1% Female BMI = 28.1 Perirenal fat = 3.57 cm CR = 1.84 cm RA = 5.67 cm	N/A	USG	Perirenal fat thickness Cutis-rectis thickness and the rectis-aorta thickness Routine serum biochemistry BMI and waist circumference

Abbreviations: BMI, Body mass index; BP, Blood pressure; cIMT, Carotid intima–media thickness; CR, Cutis-rectis thickness; CRP, C reactive protein; ECHO, Echocardiography; IA, Intra-abdominal; IP, Intraperitoneal; MDCT, Multi-detector computed tomography; MRI, Magnetic resonance imaging; *N*, Number; N/A, Not applicable; RA, Rectis-aorta thickness; RP, Retroperitoneal; SC, Subcutaneous; USG, Ultrasonography.

the assessment of lipid content of liver and pancreas all of which are correlated with the lipid content determined on biopsy specimens.[116,120,123,124] Furthermore, renal sinus lipid content is increased in pre-diabetic subjects compared to normoglycaemic subjects and is associated with a decline in eGFR. Nonetheless, no consensus has been reached in terms of protocol to be implemented in these cases and there is need for further validation studies. Sequences like spectroscopy sequences require special technical skills and additional hardware and software capabilities. Not all patients fit into MRI scanners, and many have claustrophobia. Traditional Gadolinium-based contrast agents, if indicated in a scan, is specifically contraindicated with poor GFR (typically <30 ml/min/1.73 m^2), although newer ones are safer. Many patients have legacy metal instrumentation that is ferromagnetic and would not be MRI-compatible, such as pacemakers. Even if compatible, small metallic surgical clips or other instrumentations such as lumbar spine screws can all cause artefacts that make analysis of the retroperitoneum difficult and unreliable. However, MRI has no ionizing radiation and remains of high interest for this reason. The optimal patient selection and protocols for this modality remain to be seen. Major advantages and disadvantages of each imaging method have been reviewed at Table 2.

7 | THERAPEUTIC IMPLICATIONS

However, statistically significant associations between fatty kidney and chronic kidney disease or cardio-renal outcomes do not establish causality nor guarantee the efficacy of therapeutic interventions. There is a limited number of small heterogeneous studies in human subjects that have tested lifestyle modifications. Additionally, PPAR-alpha agonists, CD36 antagonists, statins, GLP-1 receptor agonists and SGLT-2 inhibitors are potential drugs of interest at diverse stages of clinical development.

7.1 | Lifestyle modifications

In a randomized clinical trial involving 278 participants undergoing 18-months of dietary intervention with or without exercise, a statistically significant decline in renal

TABLE 2 Major advantages and disadvantages of the imaging methods for the assessment of fatty kidney

Method of choice	Advantages	Disadvantages
Ultrasonography	• Widely available • Inexpensive • Rapid assessment • Real-time point imaging option • Lack of ionizing radiation • Suitable for pregnant patients	• Operator dependent method • Poor resolution of the image • Poor imaging quality in the presence of air, bone and fat • High risk for false negative results • No clear guideline for fatty kidney assessment
Computed tomography	• High specificity and sensitivity for adipose tissue • High resolution of the image • Rapid assessment • Not operator dependent	• Use of ionizing radiation • Need for radiocontrast agent in certain methods • High cost • Not suitable for pregnant patients • No clear guideline for fatty kidney assessment
Magnetic resonance imaging	• High specificity and sensitivity for adipose tissue • Lack of ionizing radiation • High resolution of the image • Not operator dependent • Suitable for pregnant patients	• Slow assessment • Need for radiocontrast agent in certain methods • Potential need for sedation • High cost • Poor availability • No clear guideline for fatty kidney assessment
Magnetic resonance spectroscopy	• Highest sensitivity and specificity for fat quantification in a tissue • Lack of ionizing radiation or radiocontrast agent • Not operator dependent • High resolution of the image	• High cost • Poor availability • No clear guideline for fatty kidney assessment

sinus fat was documented and correlated with decrease in pericardial and hepatic adipose content and improvement in hepatic functions, whereas there was no significant improvement in renal function or blood pressure.[125]

7.2 | PPAR-alpha agonists

PPAR-alpha is involved in lipolysis and beta oxidation in renal tubular epithelium and podocytes. Significant improvement in renal oxidative stress, renal function and proteinuria has been recorded with fenofibrate in mice, but no clinical studies have yet investigated the effects of PPAR-alpha agonists on renal lipid deposition.[126] However, there is evidence supporting kidney protection by fenofibrate from large observational studies and post hoc analysis of randomized clinical trials.[127,128] In the national cohort of Taiwan's National Health Insurance Research Database, the fenofibrate group exhibited the lowest incidence of permanent dialysis (fenofibrate vs nonuser: subdistribution HR [SHR]: 0.78; 95% CI, 0.77–0.80; statins vs fenofibrate: SHR: 1.27; 95% CI, 1.26–1.29; statin-fenofibrate combination vs fenofibrate: SHR: 1.15; 95% CI, 1.13–1.17).[128] A post hoc analysis of 2636 participants in the fenofibrate arm and 2632 in the placebo arm in the ACCORD Lipid Trial disclosed that during a median follow-up of 4 years, treatment with fenofibrate was associated with lower rate of eGFR decline (−0.28 ml/min per 1.73 m^2 per year in the fenofibrate group vs. −1.25 ml/min per 1.73 m^2 per year in the placebo group, $p < 0.01$) and with lower incidence of microalbuminuria (hazard ratio [HR] 0.56, 95% confidence interval [CI] 0.43–0.72, $p < 0.001$) and macroalbuminuria (HR 0.72, 95% CI 0.57–0.91, $p < 0.001$), although there was no difference in incidence of CKD (HR 0.92, 95% CI 0.74–1.15, $p = 0.46$) and/or kidney failure (HR 0.95, 95% CI 0.68–1.33, $p = 0.76$).[127] The literature on fenofibrate is confusing, as it results in an early, transient increase in serum creatinine. Although initially thought to be related to changes in tubular creatinine secretion, it is also associated with increased serum cystatin; thus, it likely represents a haemodynamic decrease in eGFR,[129] similar to that observed with other nephroprotective drugs such as RAS blockers, SGLT-2 inhibitors, tolvaptan and finerenone.[130]

7.3 | CD36 antagonists

No studies have yet investigated the effects of CD36 antagonists in human subjects. However, CD36 is involved in the uptake of cholesterol and lipoproteins into renal tissue and CD36 antagonists had positive effects on renal inflammation and fibrosis in mice.[131,132]

7.4 | Statins

Statins are competitive inhibitors of rate-limiting steps of in vivo cholesterol synthesis, HMG-CoA reductase and decrease serum cholesterol and triglyceride levels.[133] Simvastatin in combination with ezetimibe did not improve renal function in the SHARP trial conducted over nine thousand subjects, whereas in smaller studies use of statins in patients with chronic kidney disease was associated with improved proteinuria.[36,134] Therefore, studies addressing the effects of statins on renal adipose accumulation, although, despite numerous clinical trials and observational studies, there is not yet convincing evidence of an impact on renal function.

7.5 | GLP-1 receptor agonists

Glucagon-like peptide 1 receptor agonists are widely used in the treatment of type 2 diabetes mellitus and decrease body weight.[135] Ultrasonographic examination revealed redistribution of body fat tissue and decline in adiposity in patients using GLP-1 receptor agonists, namely exenatide and liraglutide, for 3 months.[136] Furthermore, GLP-1 receptor agonists decrease the renal lipid accumulation including triglycerides, FFAs and cholesterol through restoration of balance between lipolytic and lipogenic pathways and improvement in mitochondrial function through the Sirt1/AMPK/PGC1α pathway.[137–139] Beneficial effects of GLP-1 receptor agonists on insulin sensitivity and body weight may also contribute to such effects. No studies have yet investigated the effects of GLP-1 receptor agonists on renal adipose tissue in human subjects; however, studies performed in subjects with non-alcoholic fatty liver disease treated with GLP-1 receptor agonists indicate that GLP-1 receptor agonists are effective for hepatic steatosis and inflammation, with the potential to reverse fibrosis.[140–142] In persons with type 2 diabetes, GLP-1 receptor agonists, as SGLT-2 inhibitors discussed below, improve both cardiovascular and kidney outcomes, although kidney protection from the point of view of preservation of kidney function is not as well established as for SGLT-2 inhibitors.[143]

7.6 | SGLT-2 inhibitors

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are indicated to treat type 2 diabetes mellitus and diabetic and non-diabetic chronic kidney disease or heat failure.[144–146] Hypoxia-inducible factor alpha (HIF-1-alpha), which is responsible for the metabolic switch from lipid beta oxidation to glycolysis as energy source, and thus, lipid

accumulation, is suppressed by SGLT-2 inhibitors in vitro in mice and human kidney samples.[143,147,148] SGLT-2 inhibitors also decrease weight and body mass index. Additionally, SGLT-2 inhibitors decrease the insulin-to-glucagon ratio, leading to a favourable shift in lipolysis-to-lipogenesis and glycolysis-to-gluconeogenesis ratios in terms of improvement in fatty kidney.[144,149] Although no human studies have addressed yet the impact of SGLT-2 inhibitors on fatty kidney, they are well established kidney protective drugs. Additionally, studies conducted with NAFLD patients suggest promising outcomes in patients with fatty kidney due to shared pathophysiological mechanisms.[145]

7.7 | Other potential targets

Although almost all components of adipogenesis, signal transduction and lipid metabolism have a potential to be used as therapeutic target in fatty kidney and chronic kidney disease, farnesoid X receptor (FXR) activators, antioxidants and sterol regulatory element binding protein 1 (SREBP-1) regulators of which mediate lipid biosynthesis and fibrosis appear to be the main candidates for future studies.[15,73,150] Experimental studies showed FXR activators may protects from obesity-induced kidney injury and targeting SREBP might be an important pharmacological strategy to attenuate the progression of kidney diseases.[151]

8 | CONCLUSION

Fat accumulation throughout body including various tissues and organs is commonly encountered, especially in overweight and obese individuals mainly due to insulin resistance. Fatty kidney, as an emerging area of nephrology research, is a concept with multiple clinical consequences such as albuminuria, decline in eGFR and increase in the incidence of CKD. Multiple therapeutic alternatives including lifestyle modifications, PPAR-alpha agonists, statins, GLP-1 agonists, SGLT-2 inhibitors, CD36 antagonists and FXR agonists have been proposed in the treatment of fatty kidney without any consensus on the exact algorithm. The requirement for future studies investigating the pathophysiology, clinical outcomes and therapeutics of fatty kidney is clear.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Sidar Copur, Atalay Demiray and Mehmet Kanbay contributed substantially to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work. Alan Sag, Sidar Copur, Alberto Ortiz, Adrian Covic, Mehmet Kanbay and Katherine R. Tuttle drafted the work or revised it critically for important intellectual content.

ORCID

Mehmet Kanbay https://orcid.org/0000-0002-1297-0675
Atalay Demiray https://orcid.org/0000-0001-5503-5305

REFERENCES

1. Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. *Ther Adv Cardiovasc Dis*. 2017;11:215-225.
2. Eckel RH, Alberti KG, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2010;375:181-183.
3. Ford ES. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the US. *Diabetes Care*. 2005;28:2745-2749.
4. Kanbay M, Bulbul MC, Copur S, et al. Therapeutic implications of shared mechanisms in non-alcoholic fatty liver disease and chronic kidney disease. *J Nephrol*. 2021;34:649-659.
5. Després JP, Lemieux I, Bergeron J, et al. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. *Arterioscler Thromb Vasc Biol*. 2008;28:1039-1049.
6. Neeland IJ, Poirier P, Després J-P. Cardiovascular and metabolic heterogeneity of obesity: clinical challenges and implications for management. *Circulation*. 2018;137:1391-1406.
7. Bays HE. Adiposopathy is "sick fat" a cardiovascular disease? *J Am Coll Cardiol*. 2011;57:2461-2473.
8. de Vries APJ, Ruggenenti P, Ruan XZ, et al. Fatty kidney: emerging role of ectopic lipid in obesity-related renal disease. *Lancet Diabetes Endocrinol*. 2014;2:417-426.
9. Artunc F, Schleicher E, Weigert C, Fritsche A, Stefan N, Haering H-U. The impact of insulin resistance on the kidney and vasculature. *Nat Rev Nephrol*. 2016;12:721-737.
10. Xie K, Bao L, Jiang X, et al. The association of metabolic syndrome components and chronic kidney disease in patients with hypertension. *Lipids Health Dis*. 2019;18:1-6.
11. Chen J, Muntner P, Hamm LL, et al. The metabolic syndrome and chronic kidney disease in US adults. *Ann Intern Med*. 2004;140:167-174.
12. Yerlikaya A, Dagel T, King C, et al. Dietary and commercialized fructose: sweet or sour? *Int Urol Nephrol*. 2017;49:1611-1620.
13. Lin Y-C, Chang Y-H, Yang S-Y, Wu K-D, Chu T-S. Update of pathophysiology and management of diabetic kidney disease. *J Formos Med Assoc*. 2018;117:662-675.
14. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. *Clin J Am Soc Nephrol*. 2017;12:2032-2045.
15. Jiang T, Wang Z, Proctor G, et al. Diet-induced obesity in C57BL/6J mice causes increased renal lipid accumulation and glomerulosclerosis via a sterol regulatory element-binding protein-1c-dependent pathway. *J Biol Chem*. 2005;280:32317-32325.
16. Wahba IM, Mak RH. Obesity and obesity-initiated metabolic syndrome: mechanistic links to chronic kidney disease. *Clin J Am Soc Nephrol*. 2007;2:550-562.

17. Wang XX, Jiang T, Shen Y, et al. The farnesoid X receptor modulates renal lipid metabolism and diet-induced renal inflammation, fibrosis, and proteinuria. *Am J Physiol Renal Physiol*. 2009;297:F1587-F1596.
18. Dominguez J, Wu P, Packer CS, Temm C, Kelly KJ. Lipotoxic and inflammatory phenotypes in rats with uncontrolled metabolic syndrome and nephropathy. *Am J Physiol Renal Physiol*. 2007;293:F670-F679.
19. Proctor G, Jiang T, Iwahashi M, Wang Z, Li J, Levi M. Regulation of renal fatty acid and cholesterol metabolism, inflammation, and fibrosis in Akita and OVE26 mice with type 1 diabetes. *Diabetes*. 2006;55:2502-2509.
20. Gai Z, Wang T, Visentin M, Kullak-Ublick GA, Fu X, Wang Z. Lipid accumulation and chronic kidney disease. *Nutrients*. 2019;11:722.
21. Susztak K, Ciccone E, McCue P, Sharma K, Böttinger EP. Multiple metabolic hits converge on CD36 as novel mediator of tubular epithelial apoptosis in diabetic nephropathy. *PLoS Med*. 2005;2:e45.
22. Okamura DM, López-Guisa JM, Koelsch K, Collins S, Eddy AA. Atherogenic scavenger receptor modulation in the tubulointerstitium in response to chronic renal injury. *Am J Physiol Renal Physiol*. 2007;293:F575-F585.
23. Hua W, Huang H-Z, Tan L-T, et al. CD36 mediated fatty acid-induced podocyte apoptosis via oxidative stress. *PLoS One*. 2015;10(5):e0127507.
24. Ruan XZ, Varghese Z, Powis SH, Moorhead JF. Human mesangial cells express inducible macrophage scavenger receptor. *Kidney Int*. 1999;56:440-451.
25. Nicholson AC, Febbraio M, Han J, Silverstein RL, Hajjar DP. CD36 in atherosclerosis: the role of a class B macrophage scavenger receptor. *Ann N Y Acad Sci*. 2000;902:128-133.
26. Kennedy DJ, Chen Y, Huang W, et al. CD36 and Na/K-ATPase-α1 form a proinflammatory signaling loop in kidney. *Hypertension*. 2013;61:216-224.
27. Accessed December 23. https://gnomad.broadinstitute.org/gene/ENSG00000135218?dataset=gnomad_r2_1
28. Yang X, Okamura DM, Lu X, et al. CD36 in chronic kidney disease: novel insights and therapeutic opportunities. *Nat Rev Nephrol*. 2017;13:769-781.
29. Tontonoz P, Nagy L, Alvarez JG, Thomazy VA, Evans RM. PPARγ promotes monocyte/macrophage differentiation and uptake of oxidized LDL. *Cell*. 1998;93:241-252.
30. Bige N, Shweke N, Benhassine S, et al. Thrombospondin-1 plays a profibrotic and pro-inflammatory role during ureteric obstruction. *Kidney Int*. 2012;81:1226-1238.
31. Cui W, Maimaitiyiming H, Zhou Q, Norman H, Zhou C, Wang S. Interaction of thrombospondin1 and CD36 contributes to obesity-associated podocytopathy. *Biochim Biophys Acta*. 2015;1852:1323-1333.
32. Okamura DM, Pennathur S, Pasichnyk K, et al. CD36 regulates oxidative stress and inflammation in hypercholesterolemic CKD. *J Am Soc Nephrol*. 2009;20:495-505.
33. Wahl P, Ducasa GM, Fornoni A. Systemic and renal lipids in kidney disease development and progression. *Am J Physiol Renal Physiol*. 2016;310:F433-F445.
34. Holdaas H, Fellström B, Jardine AG, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet*. 2003;361:2024-2031.
35. Hu P-J, Wu M-Y, Lin T-C, et al. Effect of statins on renal function in chronic kidney disease patients. *Sci Rep*. 2018;8:1-7.
36. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011;377:2181-2192.
37. Liu B, Ramirez CM, Miller AM, Repa JJ, Turley SD, Dietschy JM. Cyclodextrin overcomes the transport defect in nearly every organ of NPC1 mice leading to excretion of sequestered cholesterol as bile acid. *J Lipid Res*. 2010;51:933-944.
38. Gutwein P, Abdel-Bakky MS, Schramme A, et al. CXCL16 is expressed in podocytes and acts as a scavenger receptor for oxidized low-density lipoprotein. *Am J Pathol*. 2009;174:2061-2072.
39. Lee HS. Mechanisms and consequences of hypertriglyceridemia and cellular lipid accumulation in chronic kidney disease and metabolic syndrome. *Histol Histopathol*. 2011;26(12):1599-1610.
40. Afshinnia F, Rajendiran TM, Soni T, et al. Impaired β-oxidation and altered complex lipid fatty acid partitioning with advancing CKD. *J Am Soc Nephrol*. 2018;29:295-306.
41. Sieber J, Lindenmeyer MT, Kampe K, et al. Regulation of podocyte survival and endoplasmic reticulum stress by fatty acids. *Am J Physiol Renal Physiol*. 2010;299:F821-F829.
42. Sieber J, Weins A, Kampe K, et al. Susceptibility of podocytes to palmitic acid is regulated by stearoyl-CoA desaturases 1 and 2. *Am J Pathol*. 2013;183:735-744.
43. Duchateau PN, Pullinger CR, Orellana RE, et al. Apolipoprotein L, a new human high density lipoprotein apolipoprotein expressed by the pancreas: Identification, cloning, characterization, and plasma distribution of apolipoprotein L. *J Biol Chem*. 1997;272:25576-25582.
44. Madhavan SM, O'Toole JF, Konieczkowski M, Ganesan S, Bruggeman LA, Sedor JR. APOL1 localization in normal kidney and nondiabetic kidney disease. *J Am Soc Nephrol*. 2011;22:2119-2128.
45. Rust S, Rosier M, Funke H, et al. Tangier disease is caused by mutations in the gene encoding ATP-binding cassette transporter 1. *Nat Genet*. 1999;22:352-355.
46. Tang C, Kanter JE, Bornfeldt KE, Leboeuf RC, Oram JF. Diabetes reduces the cholesterol exporter ABCA1 in mouse macrophages and kidneys 1. *J Lipid Res*. 2010;51:1719-1728.
47. Mohamed MMB, Velez JCQ. Proteinuria in COVID-19. *Clin Kidney J*. 2021;14:i40-i47.
48. Couturier A, Ferlicot S, Chevalier K, et al. Indirect effects of severe acute respiratory syndrome coronavirus 2 on the kidney in coronavirus disease patients. *Clin Kidney J*. 2020;13:347-353.
49. Xue C, Nie W, Tang D, Yi L, Mei C. Apolipoprotein E gene variants on the risk of end stage renal disease. *PLoS One*. 2013;8:e83367.
50. Bruschi M, Catarsi P, Candiano G, et al. Apolipoprotein E in idiopathic nephrotic syndrome and focal segmental glomerulosclerosis. *Kidney Int*. 2003;63:686-695.
51. Ohta Y, Yamamoto S-I, Tsuchida H, et al. Nephropathy of familial lecithin-cholesterol acyltransferase deficiency: report of a case. *Am J Kidney Dis*. 1986;7:41-46.
52. Lambert G, Sakai N, Vaisman BL, et al. Analysis of glomerulosclerosis and atherosclerosis in

lecithin cholesterol acyltransferase-deficient mice. *J Biol Chem*. 2001;276:15090-15098.
53. Mende CW, Einhorn D. Fatty kidney disease: a new renal and endocrine clinical entity? Describing the role of the kidney in obesity, metabolic syndrome, and type 2 diabetes. *Endocr Pract*. 2019;25:854-858.
54. Opazo-Ríos L, Mas S, Marín-Royo G, et al. Lipotoxicity and diabetic nephropathy: novel mechanistic insights and therapeutic opportunities. *Int J Mol Sci*. 2020;21:2632.
55. Sun L, Halaihel N, Zhang W, Rogers T, Levi M. Role of sterol regulatory element-binding protein 1 in regulation of renal lipid metabolism and glomerulosclerosis in diabetes mellitus. *J Biol Chem*. 2002;277:18919-18927.
56. Fang Y, Xu Y, Yang Y, Liu C, Zhao D, Ke J. The relationship between perirenal fat thickness and reduced glomerular filtration rate in patients with type 2 diabetes. *J Diabetes Res*. 2020;2020:1-7.
57. Hammoud SH, AlZaim I, Al-Dhaheri Y, Eid AH, El-Yazbi AF. Perirenal adipose tissue inflammation: novel insights linking metabolic dysfunction to renal diseases. *Front Endocrinol*. 2021;12:707126.
58. Huang N, Mao E-W, Hou N-N, Liu Y-P, Han F, Sun X-D. Novel insight into perirenal adipose tissue: a neglected adipose depot linking cardiovascular and chronic kidney disease. *World J Diabetes*. 2020;11:115-125.
59. Lin L, Dekkers IA, Huang L, et al. Renal sinus fat volume in type 2 diabetes mellitus is associated with glycated hemoglobin and metabolic risk factors. *J Diabetes Complications*. 2021;35:107973.
60. Ruan XZ, Varghese Z, Moorhead JF. An update on the lipid nephrotoxicity hypothesis. *Nat Rev Nephrol*. 2009;5:713-721.
61. Davidson A, Hartman D, Choyke P, Wagner B. Renal sinus and periureteral abnormalities. *Davidson's radiology of the kidney and genitourinary tract*. 3rd ed. Saunders; 1999:431-455.
62. Rha SE, Byun JY, Jung SE, et al. The renal sinus: pathologic spectrum and multimodality imaging approach. *Radiographics*. 2004;24:S117-S131.
63. Liu B-X, Sun W, Kong X-Q. Perirenal fat: a unique fat pad and potential target for cardiovascular disease. *Angiology*. 2019;70:584-593.
64. Yang P, Xiao Y, Luo X, et al. Inflammatory stress promotes the development of obesity-related chronic kidney disease via CD36 in mice. *J Lipid Res*. 2017;58:1417-1427.
65. Lau WB, Ohashi K, Wang Y, et al. Role of adipokines in cardiovascular disease. *Circ J*. 2017;81:920-928.
66. Montani J-P, Carroll JF, Dwyer TM, Antic V, Yang Z, Dulloo AG. Ectopic fat storage in heart, blood vessels and kidneys in the pathogenesis of cardiovascular diseases. *Int J Obesity*. 2004;28:S58-S65.
67. Declèves AE, Mathew AV, Cunard R, Sharma K. AMPK mediates the initiation of kidney disease induced by a high-fat diet. *J Am Soc Nephrol*. 2011;22:1846-1855.
68. Kang HM, Ahn SH, Choi P, et al. Defective fatty acid oxidation in renal tubular epithelial cells has a key role in kidney fibrosis development. *Nat Med*. 2015;21:37-46.
69. Miyamoto S, Hsu CC, Hamm G, et al. Mass spectrometry imaging reveals elevated glomerular ATP/AMP in diabetes/obesity and identifies sphingomyelin as a possible mediator. *EBioMedicine*. 2016;7:121-134.
70. Koch RE, Josefson CC, Hill GE. Mitochondrial function, ornamentation, and immunocompetence. *Biol Rev Camb Philos Soc*. 2017;92:1459-1474.
71. Houten SM, Violante S, Ventura FV, Wanders RJ. The biochemistry and physiology of mitochondrial fatty acid β-oxidation and its genetic disorders. *Annu Rev Physiol*. 2016;78:23-44.
72. Mandel LJ. Metabolic substrates, cellular energy production, and the regulation of proximal tubular transport. *Annu Rev Physiol*. 1985;47:85-101.
73. Wang XX, Jiang T, Shen Y, et al. Diabetic nephropathy is accelerated by farnesoid X receptor deficiency and inhibited by farnesoid X receptor activation in a type 1 diabetes model. *Diabetes*. 2010;59:2916-2927.
74. Forbes JM, Thorburn DR. Mitochondrial dysfunction in diabetic kidney disease. *Nat Rev Nephrol*. 2018;14:291-312.
75. Jang HS, Noh MR, Kim J, Padanilam BJ. Defective mitochondrial fatty acid oxidation and lipotoxicity in kidney diseases. *Front Med*. 2020;7:65.
76. Adeosun SO, Gordon DM, Weeks MF, et al. Loss of biliverdin reductase-A promotes lipid accumulation and lipotoxicity in mouse proximal tubule cells. *Am J Physiol Renal Physiol*. 2018;315:F323-f331.
77. Kanbay M, Demiray A, Afsar B, et al. Role of klotho in the development of essential hypertension. *Hypertension*. 2021;77:740-750.
78. Sastre C, Rubio-Navarro A, Buendia I, et al. Hyperlipidemia-associated renal damage decreases Klotho expression in kidneys from ApoE knockout mice. *PLoS One*. 2013;8:e83713.
79. Buendia P, Carracedo J, Soriano S, et al. Klotho prevents NFkappaB translocation and protects endothelial cell from senescence induced by uremia. *J Gerontol A Biol Sci Med Sci*. 2015;70:1198-1209.
80. Kanda T, Matsuoka S, Yamazaki M, et al. Apoptosis and non-alcoholic fatty liver diseases. *World J Gastroenterol*. 2018;24:2661-2672.
81. Rives C, Fougerat A, Ellero-Simatos S, et al. Oxidative stress in NAFLD: role of nutrients and food contaminants. *Biomolecules*. 2020;10.
82. Combs TP, Marliss EB. Adiponectin signaling in the liver. *Rev Endocr Metab Disord*. 2014;15:137-147.
83. Cernea S, Roiban AL, Both E, Huţanu A. Serum leptin and leptin resistance correlations with NAFLD in patients with type 2 diabetes. *Diabetes Metab Res Rev*. 2018;34:e3050.
84. Boutari C, Mantzoros CS. Adiponectin and leptin in the diagnosis and therapy of NAFLD. *Metabolism*. 2020;103:154028.
85. Bungau S, Behl T, Tit DM, et al. Interactions between leptin and insulin resistance in patients with prediabetes, with and without NAFLD. *Exp Ther Med*. 2020;20:197.
86. Shabalala SC, Dludla PV, Mabasa L, et al. The effect of adiponectin in the pathogenesis of non-alcoholic fatty liver disease (NAFLD) and the potential role of polyphenols in the modulation of adiponectin signaling. *Biomed Pharmacother*. 2020;131:110785.
87. Kanbay M, Onal EM, Afsar B, et al. The crosstalk of gut microbiota and chronic kidney disease: role of inflammation, proteinuria, hypertension, and diabetes mellitus. *Int Urol Nephrol*. 2018;50:1453-1466.
88. Onal EM, Afsar B, Covic A, Vaziri ND, Kanbay M. Gut microbiota and inflammation in chronic kidney disease and their roles

in the development of cardiovascular disease. *Hypertens Res*. 2019;42:123-140.
89. Castillo-Rodriguez E, Fernandez-Prado R, Esteras R, et al. Impact of altered intestinal microbiota on chronic kidney disease progression. *Toxins*. 2018;10:300.
90. Mosterd CM, Kanbay M, van den Born BJH, van Raalte DH, Rampanelli E. Intestinal microbiota and diabetic kidney diseases: the role of microbiota and derived metabolites inmodulation of renal inflammation and disease progression. *Best Pract Res Clin Endocrinol Metab*. 2021;35:101484.
91. Musso G, Cassader M, Gambino R. PNPLA3 rs738409 and TM6SF2 rs58542926 gene variants affect renal disease and function in nonalcoholic fatty liver disease. *Hepatology*. 2015;62:658-659.
92. Oniki K, Saruwatari J, Izuka T, et al. Influence of the PNPLA3 rs738409 polymorphism on non-alcoholic fatty liver disease and renal function among normal weight subjects. *PLoS One*. 2015;10:e0132640.
93. Targher G, Mantovani A, Alisi A, et al. Relationship between PNPLA3 rs738409 polymorphism and decreased kidney function in children with NAFLD. *Hepatology*. 2019;70:142-153.
94. Marzuillo P, Di Sessa A, Guarino S, et al. Nonalcoholic fatty liver disease and eGFR levels could be linked by the PNPLA3 I148M polymorphism in children with obesity. *Pediatr Obes*. 2019;14:e12539.
95. Di Costanzo A, Pacifico L, D'Erasmo L, et al. Nonalcoholic Fatty Liver Disease (NAFLD), but not its susceptibility gene variants, influences the decrease of kidney function in overweight/obese children. *Int J Mol Sci*. 2019;20:4444.
96. Sun DQ, Zheng KI, Xu G, et al. PNPLA3 rs738409 is associated with renal glomerular and tubular injury in NAFLD patients with persistently normal ALT levels. *Liver Int*. 2020;40:107-119.
97. Mantovani A, Taliento A, Zusi C, et al. PNPLA3 I148M gene variant and chronic kidney disease in type 2 diabetic patients with NAFLD: clinical and experimental findings. *Liver Int*. 2020;40:1130-1141.
98. Trasino SE, Tang XH, Shevchuk MM, Choi ME, Gudas LJ. Amelioration of diabetic nephropathy using a retinoic acid receptor β2 agonist. *J Pharmacol Exp Ther*. 2018;367:82-94.
99. Foster MC, Hwang SJ, Porter SA, Massaro JM, Hoffmann U, Fox CS. Fatty kidney, hypertension, and chronic kidney disease: the Framingham Heart Study. *Hypertension*. 2011;58:784-790.
100. Spit KA, Muskiet MHA, Tonneijck L, et al. Renal sinus fat and renal hemodynamics: a cross-sectional analysis. *Magma*. 2020;33:73-80.
101. Chughtai HL, Morgan TM, Rocco M, et al. Renal sinus fat and poor blood pressure control in middle-aged and elderly individuals at risk for cardiovascular events. *Hypertension*. 2010;56:901-906.
102. Xu T, Sheng Z, Yao L. Obesity-related glomerulopathy: pathogenesis, pathologic, clinical characteristics and treatment. *Front Med*. 2017;11:340-348.
103. Bassols J, Martínez-Calcerrada JM, Prats-Puig A, et al. Perirenal fat is related to carotid intima-media thickness in children. *Int J Obes*. 2018;42:641-647.
104. Manno C, Campobasso N, Nardecchia A, et al. Relationship of para- and perirenal fat and epicardial fat with metabolic parameters in overweight and obese subjects. *Eat Weight Disord*. 2019;24:67-72.
105. Geraci G, Zammuto MM, Mattina A, et al. Para-perirenal distribution of body fat is associated with reduced glomerular filtration rate regardless of other indices of adiposity in hypertensive patients. *J Clin Hypertens*. 2018;20:1438-1446.
106. López-Bermejo A, Prats-Puig A, Osiniri I, Martínez-Calcerrada JM, Bassols J. Perirenal and epicardial fat and their association with carotid intima-media thickness in children. *Ann Pediatr Endocrinol Metab*. 2019;24:220-225.
107. Grigoraș A, Balan RA, Căruntu ID, et al. Perirenal adipose tissue-current knowledge and future opportunities. *J Clin Med*. 2021;10:1291.
108. Byambasukh O, Eisenga MF, Gansevoort RT, Bakker SJ, Corpeleijn E. Body fat estimates from bioelectrical impedance equations in cardiovascular risk assessment: the PREVEND cohort study. *Eur J Prev Cardiol*. 2019;26:905-916.
109. D'Marco L, Puchades MJ, Panizo N, et al. Cardiorenal fat: a cardiovascular risk factor with implications in chronic kidney disease. *Front Med*. 2021;8:640814.
110. Arnardottir ES, Mackiewicz M, Gislason T, Teff KL, Pack AI. Molecular signatures of obstructive sleep apnea in adults: a review and perspective. *Sleep*. 2009;32:447-470.
111. Targher G, Byrne CD. Non-alcoholic fatty liver disease: an emerging driving force in chronic kidney disease. *Nat Rev Nephrol*. 2017;13:297-310.
112. Marchington JM, Mattacks CA, Pond CM. Adipose tissue in the mammalian heart and pericardium: structure, foetal development and biochemical properties. *Comp Biochem Physiol B*. 1989;94:225-232.
113. D'Marco L, Puchades MJ, Gorriz JL, et al. Epicardial adipose tissue, adiponectin and leptin: a potential source of cardiovascular risk in chronic kidney disease. *Int J Mol Sci*. 2020;21:978.
114. Gong W, Ren H, Tong H, et al. A comparison of ultrasound and magnetic resonance imaging to assess visceral fat in the metabolic syndrome. *Asia Pac J Clin Nutr*. 2007;16:339-345.
115. Armellini F, Zamboni M, Robbi R, et al. Total and intra-abdominal fat measurements by ultrasound and computerized tomography. *Int J Obes Relat Metab Disord*. 1993;17:209-214.
116. Wong VW-S, Wong GL-H, Yeung DK-W, et al. Fatty pancreas, insulin resistance, and β-cell function: a population study using fat-water magnetic resonance imaging. *Am J Gastroenterol*. 2014;109:589-597.
117. Xia MF, Yan HM, He WY, et al. Standardized ultrasound hepatic/renal ratio and hepatic attenuation rate to quantify liver fat content: an improvement method. *Obesity*. 2012;20:444-452.
118. von Volkmann HL, Havre RF, Løberg EM, et al. Quantitative measurement of ultrasound attenuation and hepato-renal index in non-alcoholic fatty liver disease. *Med Ultrason*. 2013;15:16-22.
119. Favre G, Grangeon-Chapon C, Raffaelli C, François-Chalmin F, Iannelli A, Esnault V. Perirenal fat thickness measured with computed tomography is a reliable estimate of perirenal fat mass. *PLoS One*. 2017;12:e0175561.
120. Idilman IS, Tuzun A, Savas B, et al. Quantification of liver, pancreas, kidney, and vertebral body MRI-PDFF in non-alcoholic fatty liver disease. *Abdom Imaging*. 2015;40:1512-1519.
121. Jonker JT, de Heer P, Engelse MA, et al. Metabolic imaging of fatty kidney in diabesity: validation and dietary intervention. *Nephrol Dial Transplant*. 2018;33:224-230.

122. Notohamiprodjo M, Goepfert M, Will S, et al. Renal and renal sinus fat volumes as quantified by magnetic resonance imaging in subjects with prediabetes, diabetes, and normal glucose tolerance. *PLoS One*. 2020;15:e0216635.
123. Noureddin M, Lam J, Peterson MR, et al. Utility of magnetic resonance imaging versus histology for quantifying changes in liver fat in nonalcoholic fatty liver disease trials. *Hepatology*. 2013;58:1930-1940.
124. Semelka RC, Ascher S. MR imaging of the pancreas. *Radiology*. 1993;188:593-602.
125. Zelicha H, Schwarzfuchs D, Shelef I, et al. Changes of renal sinus fat and renal parenchymal fat during an 18-month randomized weight loss trial. *Clin Nutr*. 2018;37:1145-1153.
126. Tanaka Y, Kume S, Araki S, et al. Fenofibrate, a PPARα agonist, has renoprotective effects in mice by enhancing renal lipolysis. *Kidney Int*. 2011;79:871-882.
127. Frazier R, Mehta R, Cai X, et al. Associations of fenofibrate therapy with incidence and progression of CKD in patients With type 2 diabetes. *Kidney Int Rep*. 2019;4:94-102.
128. Yen CL, Fan PC, Lin MS, et al. Fenofibrate delays the need for dialysis and reduces cardiovascular risk among patients with advanced CKD. *J Clin Endocrinol Metab*. 2021;106:1594-1605.
129. Mychaleckyj JC, Craven T, Nayak U, et al. Reversibility of fenofibrate therapy-induced renal function impairment in ACCORD type 2 diabetic participants. *Diabetes Care*. 2012;35:1008-1014.
130. Ortiz A, Ferro CJ, Balafa O, et al. Mineralocorticoid receptor antagonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. *Nephrol Dial Transplant*. 2021.
131. Bessi VL, Labbé SM, Huynh DN, et al. EP 80317, a selective CD36 ligand, shows cardioprotective effects against post-ischaemic myocardial damage in mice. *Cardiovasc Res*. 2012;96:99-108.
132. Souza AC, Bocharov AV, Baranova IN, et al. Antagonism of scavenger receptor CD36 by 5A peptide prevents chronic kidney disease progression in mice independent of blood pressure regulation. *Kidney Int*. 2016;89(4):809-822.
133. Koch CG. Statin therapy. *Curr Pharm Des*. 2012;18:6284-6290.
134. Hu PJ, Wu MY, Lin TC, et al. Effect of statins on renal function in chronic kidney disease patients. *Sci Rep*. 2018;8:16276.
135. Greco EV, Russo G, Giandalia A, Viazzi F, Pontremoli R, De Cosmo S. GLP-1 receptor agonists and kidney protection. *Medicina*. 2019;55(6):233.
136. Morano S, Romagnoli E, Filardi T, et al. Short-term effects of glucagon-like peptide 1 (GLP-1) receptor agonists on fat distribution in patients with type 2 diabetes mellitus: an ultrasonography study. *Acta Diabetol*. 2015;52:727-732.
137. Wang C, Li L, Liu S, et al. GLP-1 receptor agonist ameliorates obesity-induced chronic kidney injury via restoring renal metabolism homeostasis. *PLoS One*. 2018;13:e0193473.
138. Zhang Y, Liu S, Fan C, et al. Effect of glucagon-like peptide 1 receptor agonists on body fat redistribution and muscle mass in overweight and obese type 2 diabetic patients. *Nan Fang Yi Ke Da Xue Xue Bao*. 2019;39:450-455.
139. Mosterd CM, Bjornstad P, van Raalte DH. Nephroprotective effects of GLP-1 receptor agonists: where do we stand? *J Nephrol*. 2020;33:965-975.
140. Seghieri M, Christensen AS, Andersen A, Solini A, Knop FK, Vilsbøll T. Future perspectives on GLP-1 receptor agonists and GLP-1/glucagon receptor Co-agonists in the treatment of NAFLD. *Front Endocrinol*. 2018;9:649.
141. Lv X, Dong Y, Hu L, Lu F, Zhou C, Qin S. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) for the management of nonalcoholic fatty liver disease (NAFLD): a systematic review. *Endocrinol Diabetes Metab*. 2020;3:e00163.
142. Ertuglu LA, Porrini E, Hornum M, et al. Glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors for diabetes after solid organ transplantation. *Transpl Int*. 2021;34:1341-1359.
143. Kanbay M, Demiray A, Afsar B, et al. Sodium-glucose cotransporter 2 inhibitors for diabetes mellitus control after kidney transplantation: review of the current evidence. *Nephrology*. 2021;26:1007-1017.
144. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia*. 2018;61:2108-2117.
145. Cherney DZ, Kanbay M, Lovshin JA. Renal physiology of glucose handling and therapeutic implications. *Nephrol Dial Transplant*. 2020;35:i3-i12.
146. Fernandez-Fernandez B, Sarafidis P, Kanbay M, et al. SGLT2 inhibitors for non-diabetic kidney disease: drugs to treat CKD that also improve glycaemia. *Clin Kidney J*. 2020;13:728-733.
147. Chang YK, Choi H, Jeong JY, et al. Dapagliflozin, SGLT2 inhibitor, attenuates renal ischemia-reperfusion injury. *PLoS One*. 2016;11:e0158810.
148. Cai T, Ke Q, Fang Y, et al. Sodium-glucose cotransporter 2 inhibition suppresses HIF-1α-mediated metabolic switch from lipid oxidation to glycolysis in kidney tubule cells of diabetic mice. *Cell Death Dis*. 2020;11:390.
149. Szekeres Z, Toth K, Szabados E. The effects of SGLT2 inhibitors on lipid metabolism. *Metabolites*. 2021;11:87.
150. Cho H, Um J, Lee JH, et al. ENOblock, a unique small molecule inhibitor of the non-glycolytic functions of enolase, alleviates the symptoms of type 2 diabetes. *Sci Rep*. 2017;7:44186.
151. Gai Z, Gui T, Hiller C, Kullak-Ublick GA. Farnesoid X receptor protects against kidney injury in uninephrectomized obese mice. *J Biol Chem*. 2016;291:2397-2411.

How to cite this article: Kanbay M, Copur S, Demiray A, et al. Fatty kidney: A possible future for chronic kidney disease research. *Eur J Clin Invest*. 2022;52:e13748. doi:10.1111/eci.13748