REVIEW

The Fatty Kidney and Beyond: A Silent Epidemic

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ABSTRACT

As the prevalence of obesity rises in the United States, so does the incidence of obesity-related kidney disease. Obesity itself is an independent risk factor for chronic kidney disease where the pathophysiology is complex, involving altered hemodynamics, renin-angiotensin-aldosterone system overactivation, and adipokines leading to inflammation and fibrosis. Obesity-related kidney disease comprises both obesity-related glomerulopathy and fatty kidney disease. Obesity-related glomerulopathy is a consequence of glomerular hyperfiltration and often presents clinically with subnephrotic proteinuria and pathologically with glomerulomegaly with or without focal glomerulosclerosis. Fatty kidney disease is the effect of renal ectopic fat contributing to chronic kidney disease. Whether the renal ectopic fat is a distinct clinical entity or a pathologic mechanism contributing to obesity-related glomerulopathy, the treatment paradigm of weight and proteinuria reduction remains the same. We present the pathophysiology behind obesity-related kidney disease, clinical outcomes, and treatment strategies, which include lifestyle interventions, use of renin-angiotensin-aldosterone system inhibitors, glucagon-like peptide 1 receptor agonists, sodium-glucose co-transporter-2 inhibitors, and bariatric surgery. With old and novel therapeutics, we are attempting to stave off the silent epidemic that obesity-related kidney disease is becoming.

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KEYWORDS: Apolipoprotein L1; Chronic kidney disease; Fatty kidney disease; Obesity; Obesity-related glomerulomegaly

INTRODUCTION

A recent study from the World Health Organization from 2022 stated that 60% of people in Europe can be classified as overweight or obese[1] and the number is also on the rise in the United States due to unhealthy dietary choices and sedentary lifestyles.[2] In 1974, Weisinger et al reported a possible link between reversible proteinuria and renal venous hypertension arising from massive obesity.[3] Further studies over the past few decades have also provided strong proof of a potential role of obesity in the pathophysiology of glomerulopathy and focal segmental glomerulosclerosis (FSGS), which was described as obesity-related glomerulopathy.[4] However, as most cases do not undergo a conclusive biopsy, the prevalence of the condition is believed to be heavily underestimated.[4]

The clinical significance of renal ectopic fat has been increasingly recognized over the past few decades. Similar to fatty liver disease, it was proposed that the ectopic renal fat merits a distinct clinical entity called "fatty kidney disease," as it contributes to diabetes, hypertension, and chronic kidney disease development and progression.[5] Multiple imaging modalities including sonography, computed tomography, and magnetic resonance imaging (MRI) have been utilized to quantify the renal sinus fat, pararenal and perirenal fat, and renal parenchymal fat and evaluate their pathologic associations at the level of the kidney and systemically (Table). Given that the majority of these studies are cross-sectional, only the correlation, not the causality of the renal ectopic fat and disease states could be established.

Here, we discussed the pathophysiology of obesity-related glomerulopathy, the mechanistic roles of ectopic fat in chronic kidney disease development and progression, and the available treatment options.

Obesity-related Glomerulopathy

Obesity-related glomerulopathy is pathologically described as the presence of glomerulomegaly, with or

without FSGS, in a patient having a body mass index (BMI) ≥30 kg/m^2.[4,25] The most common initial finding is isolated proteinuria.[25] Although the majority are believed to have proteinuria below 3.5mg/day, about 30% of cases can cross the nephrotic range.[4,26] About 50%-75% of patients also report hypertension, and 70%-80% have dyslipidemia.[26]

The pathophysiology of obesity-related glomerulopathy involves multiple pathways: hemodynamic changes, renin-angiotensin-aldosterone system (RAAS) activation, and inflammation and oxidative stress.[27] It is associated with glomerular hyperfiltration resulting in glomerular basement membrane expansion, podocyte hypertrophy and detachment, and eventual decrease in renal function.[27] Glomerular hyperfiltration also causes increased sodium and water reabsorption at the proximal tubules, leading to a reduced sodium delivery to the macula densa, subsequent reduction in the afferent artery resistance and tubuloglomerular feedback.[28,29] Adipose tissue has an intrinsic ability to produce components of RAAS, independent of the renal system.[30] The overactivation of RAAS in obesity further contributes to the glomerular hyperfiltration.[29]

Inflammation and oxidative stress also play a central role in obesity-related glomerulopathy.[31] Adipose tissue upregulates pro-inflammatory cytokines and mediators such as leptin, resistin, TNF-α, and IL-6, and downregulates the anti-inflammatory adiponectin, which plays a role in podocyte integrity.[32] In addition to its pro-inflammatory property, leptin induces TGF-β production, causing renal fibrosis.[27] Leptin can also activate the renal sympathetic nervous system, leading to sodium retention, systemic hypertension, and subsequent glomerular hyperfiltration.[29]

The presence of 2 apolipoprotein L1 (APOL1) risk variants G1/G2, known to increase the risks of kidney diseases such as HIV-associated nephropathy and FSGS,[33] was recently implicated in the pathogenesis of obesity-related glomerulopathy.[34] APOL1 risk variants also impair reverse cholesterol transport and downregulate cholesterol efflux transporters,[35] which is believed to be a mechanism of cholesterol accumulation in podocytes and kidney tissue.[36] Thus, obesity may serve as a "second hit" to cause obesity-related glomerulopathy in the setting of nephropathic APOL1 variants.[34]

The progression of untreated obesity-related glomerulopathy is typically indolent; however, 10%-33% of cases can result in renal failure or end-stage kidney disease (ESKD).[4,29,37,38] Obesity-related glomerulopathy patients are mostly seen in middle-aged adults, with sub-nephrotic proteinuria and normal serum albumin levels who do not progress to full nephrotic syndrome, offering a better long-term prognosis.[29]

CLINICAL SIGNIFICANCE

- Obesity-related chronic kidney disease includes obesity-related glomerulopathy and fatty-kidney disease (renal ectopic fat).
- Obesity-related glomerulopathy is a known renal complication of obesity that often presents with isolated, sub-nephrotic proteinuria.
- Glucagon-like peptide 1 receptor agonist is a preferred class of medication for weight loss. The treatment paradigm for obesity-related chronic kidney disease is weight and proteinuria reduction, which can be achieved by lifestyle modification, pharmacological treatment, and bariatric surgery.

THE ROLES OF RENAL ECTOPIC FAT

Renal Sinus Fat

The renal sinus is located at the medial aspect of the kidney and comprises the renal artery and vein, nerve, lymphatics, adipose tissue, minor and major calyces, renal pelvis, and proximal ureter (Figure).[39] It is not covered by the renal capsule,[40] subjecting the structures to compression by adipose tissue, known as renal sinus fat.[41] The mechanical compression of renal vasculature can 1) lead to hypoperfusion of renal parenchymal and tubules[42] and 2) cause outflow obstruction due to increased hydrostatic pressure.[43] As a result, the renal size and intracapsular pressure increase, leading to RAAS activation and resistant hypertension.[43] In addition, accumulation of renal sinus fat was associated with renal hypoxia, as indicated by increased expression of hypoxia-inducible factor-1α.[44] The resultant hypoxia causes damage primarily in the proximal convoluted tubules, leading to ischemic injury and production of kidney injury molecule-1 (KIM-1) (an early biomarker of renal injury) and fibroblast growth factor-21 (a marker of renal dysfunction).[45] In a murine model, chronic expression of KIM-1 leads to renal fibrosis and may pose as a link between recurrent acute injury and the development of chronic kidney disease.[46] The quantity of renal sinus fat also positively correlated with the level of KIM-1.[45]

Clinically, renal sinus fat has been consistently shown to negatively correlate with eGFR,[6,12,16,20,21] perhaps via increased afferent renal vascular resistance.[16] In the Framingham Heart Study, individuals with high renal sinus fat volume had a higher odds ratio for developing chronic kidney disease, even after adjusting for risk factors such as diabetes, hypertension, BMI, and visceral adipose tissue.[6] The ratio of renal sinus fat-to-cortical thickness was a better predictor of chronic kidney disease than the cortical thickness alone.[21] The ratio of <0.4 had a probability of 63% of developing chronic kidney disease, which increased to 85% with the ratio of >0.5.[21] In individuals at risk for diabetes, renal sinus fat is associated with exercise-induced albuminuria,[8] whereas in patients with diabetes, the renal sinus fat volume was significantly associated with urine

Table Studies Demonstrating the Association of Ectopic Renal Fat and Kidney Function

Study	Measurement	Imaging Modality	Types of Study	Study Population	Renal Outcomes
Foster et al, 2011[6]	Renal sinus fat	CT	Cross-sectional	2923 participants from Framingham Heart Study	High renal sinus fat: defined as sex-specific 90th percentiles in a healthy subsample • A higher odds ratio for chronic kidney disease measured by cystatin C-eGFR (OR 2.30; $P = .005$).
Lamacchia et al, 2011[7]	Pararenal and perirenal ultrasonic fat thickness	Ultrasound	Cross-sectional	151 Caucasian patients with type 2 diabetes mellitus from southeastern Italy	Pararenal and perirenal ultrasonic fat thickness was an independent predictor of: • eGFR measured by MDRD and CKD-EPI (r^2 0.366, $P = .001$) • Renal resistance index (r^2 0.529, $P = .005$)
Wagner et al, 2012[8]	Renal sinus fat	MRI	Cross-sectional	146 patients with high risk for type 2 diabetes mellitus (family history of diabetes, BMI > 27, impaired glucose tolerance, or history of gestational diabetes) from Southern Germany	Renal sinus fat significantly associated • with post-exercise UACR (standardized β coefficient 0.303, 95% CI, 0.091-0.55, $P = .006$)
Sun et al, 2013[9]	Pararenal and perirenal ultrasonic fat thickness	Ultrasound	Cross-sectional	67 obese patients without diabetes and hypertension and sex-matched healthy controls from China	Pararenal and perirenal ultrasonic fat thickness: • positive correlation with the urine albumin creatinine ratio (r = 0.610, $P < .01$) • could be an independent predictor of early renal damage
Geraci et al, 2018[10]	Pararenal and perirenal ultrasonic fat thickness	Ultrasound	Cross-sectional	296 Caucasian patients with essential hypertension	Pararenal and perirenal ultrasonic fat thickness: • negative correlation with eGFR (r = -0.284, $P < .001$) based on CKD-EPI • ≤ 3.725 cm had a negative predictive value of 94% for renal impairment (CKD-EPI eGFR <60) with the largest AUC of 0.7
Wang et al, 2018[11]	Renal parenchymal fat fraction	MRI	Cross-sectional	61 patients with type 2 diabetes mellitus (40 with normoalbuminuria and 21 with microalbuminuria) and 34 non-diabetic controls	Renal parenchymal fat fraction: • significantly higher in the microalbuminuric group (5.6% ± 1.3%) vs normoalbuminuric group (4.7% ± 1.1%) vs control group (4.3% ± 0.5%), $P < .001$
Zelicha et al, 2018[12]	Renal sinus fat and renal parenchymal fat	MRI	Randomized controlled trial	278 participants with abdominal obesity or dyslipidemia Randomized into 4 weight-loss interventions for 18 months: low-fat diet ± exercise and Mediterranean diet ± exercise	Higher renal sinus fat was associated with: • lower MDRD-eGFR (β= -0.15, $P = .01$) • higher urine albumin creatinine ratio (β= 0.13, $P = .03$) • After 18 months, renal sinus fat, but not renal parenchymal fat, was reduced significantly across all intervention groups (-9%, $P < .05$ vs baseline) • Reduction in renal sinus fat did not improve renal function

Table (*Continued*)

Study	Measurement	Imaging Modality	Types of Study	Study Population	Renal Outcomes
D'Marco et al, 2019[13]	Perirenal fat thickness	Ultrasound	Cross-sectional	103 patients with prior chronic kidney disease diagnoses from stages 1-5 from Venezuela	• Perirenal fat thickness was larger in chronic kidney disease patients with impaired fasting glucose compared with those without (1.10 ± 0.40 cm vs 0.85 ± 0.39 cm, P <.021). • Highest perirenal fat thickness was observed in patients with chronic kidney disease stages 4 and 5, based on eGFR using CKD-EPI
Fang et al, 2020[14]	Perirenal fat thickness	Ultrasound	Cross-sectional	171 patients with type 2 diabetes mellitus from China	• Perirenal fat thickness negatively correlated with MDRD-eGFR (r = -0.181, P < .05)
Shen et al, 2020[15]	Perirenal fat thickness	Ultrasound	Cross-sectional	89 patients with type 2 diabetes mellitus (66 with albuminuria and 23 without albuminuria) from Taiwan	• Perirenal fat thickness positively associated with the degree of albuminuria in linear regression analysis (r = 0.233, P = .03)
Spit et al, 2020[16]	Renal sinus fat	MRI	Cross-sectional	51 Caucasian males or postmenopausal females with type 2 diabetes mellitus	• Renal sinus fat negatively associated with eGFR measured by inulin (r = -0.38, P = 0.006) • Renal sinus fat positively associated with increased renal vascular resistance (r = 0.45, P = .001)
Chen et al, 2021[17]	Perirenal fat thickness	CT	Cross-sectional and longitudinal	190 patients enrolled in Chongqing Diabetes Registry (China) with type 2 diabetes mellitus without chronic kidney disease at baseline were followed for 2 years for chronic kidney disease development	• Increase in baseline perirenal fat associated with a higher incidence of chronic kidney disease development based on MDRD-eGFR (HR 1.67, 95% CI, 1.04-2.68)
Lin et al, 2021[18]	Pararenal and perirenal ultrasonic fat thickness	MRI	Cross-sectional	95 with type 2 diabetes mellitus and 51 healthy controls of West European and South Asian descent	• Renal sinus fat positively associated with urine albumin creatinine ratio in type 2 diabetes mellitus (standardized β = .27, P = 0.016) after adjustment for age, sex, and ethnicity • May contribute to the development of diabetic nephropathy
Bragina et al, 2022[19]	Pararenal fat	CT	Cross-sectional	320 patients without cardiovascular diseases from Russia	Risk of renal dysfunction significantly associated with the pararenal fat thickness (OR = 6.198, 95% CI, 1.958-19.617, P < .05) • AUC for the pararenal fat thickness >1.68 cm to predict renal dysfunction was 0.875 (sensitivity 63.2%, specificity 93.4%)

Table (*Continued*)

Study	Measurement	Imaging Modality	Types of Study	Study Population	Renal Outcomes
Moritz et al, 2022[20]	Renal sinus fat	MRI	Cross-sectional and longitudinal	74 patients with morbid obesity and 46 lean controls from Finland Follow-ups were conducted 6 months after bariatric surgery	• Renal sinus fat negatively correlated with eGFR based on CKD-EPI (r= -0.20, *P* = .03)
Schmidt et al, 2022[21]	Renal sinus fat-to-cortical thickness ratio	Ultrasound	Cross-sectional	199 patients with previous renal sonograms	• Average renal sinus fat-to-cortical ratio < 0.4 had 63% probability to develop renal failure • This probability increased to 65%-85% for the fat-to-cortical ratio between 0.4 and 0.5, and plateaued at 85% for the ratio > 0.5 • Renal sinus fat-to-cortical thickness ratio has a significant negative correlation with eGFR for the left kidney and is a better predictor of chronic kidney disease progression than cortical thickness alone
Shen et al, 2022[22]	Renal parenchymal fat fraction	MRI	Cross-sectional	189 subjects with type 2 diabetes mellitus from China	• Patients with highest tertile of renal parenchymal fat fraction had the highest risk for chronic kidney disease (eGFR from EPI-CKD) compared with those with the lowest tertile (OR 3.98%, CI 1.12-14.09, *P* = .032)
Spurny et al, 2022[23]	Renal sinus fat and renal cortex fat	MRI	Randomized controlled trial	137 obese or overweight non-smokers were randomized to intermittent calorie restriction, continuous calorie restriction, or the control group	• Dietary weight loss reduced renal sinus fat but not renal cortex fat • Small improvements in creatinine were noted at week 12 (-2.5%, *P* = .02) but not at week 50
Tastemur et al, 2022[24]	Perirenal fat volume	CT	Retrospective	54 living kidney donors and recipients	• AUC of perirenal fat volume to predict MDRD-eGFR<60 of recipients in the 12th month was 0.710 (*P* = .02) • Donor's perirenal fat volume is an independent risk factor for the recipient's low eGFR

AUC = area under the receiver operating characteristic curve; BMI = body mass index; CKD-EPI = chronic kidney disease epidemiology collaboration; CI = confidence interval; CT = computed tomography; eGFR = estimated glomerular filtration rate; HR = hazard ratio; MDRD = modification of diet in renal disease, MRI = magnetic resonance imaging, OR = odds ratio; UACR = urine albumin-to-creatinine ratio.

albumin-to-creatinine ratio, implying that renal sinus fat may either play a role or be an early indicator of diabetic nephropathy.[18] Despite a strong association between renal sinus fat and chronic kidney disease, it is unclear whether the reduction in renal sinus fat could improve renal function. Limited randomized control trials (RCTs) with non-surgical weight-loss interventions showed either no or minimal improvement in renal function despite a significant reduction in renal sinus fat quantified by MRI.[12,23]

Pararenal and Perirenal Fat

The pararenal fat is the adipose tissue layer surrounding the kidney outside of the Gerota's fascia, and the perirenal fat is located between the renal capsule and the Gerota's fascia (Figure). Pararenal and perirenal fat separately and together correlated positively with hypertension,[47,48] insulin resistance,[47,48] hemoglobin A1c,[47,9,15] albuminuria,[47,9,15] metabolic syndrome,[49] and chronic kidney disease.[7,10,14,17,19] The reduction of perirenal fat after sleeve-gastrectomy was associated with the reduction in the number of anti-hypertensive medications or remission of hypertension.[47] Even in obese patients without hypertension and diabetes, the pararenal and perirenal fat thickness was correlated positively with urine albumin-to-creatinine ratio and could be an independent predictor of early renal damage.[9] The pararenal and perirenal ultrasonic fat thickness increases in size as chronic kidney disease progresses with the highest perirenal ultrasonic fat thickness found in chronic kidney disease stages 4 and 5.[13] In renal transplantation, the living donors' perirenal fat volume affects long-term graft function, as it was an independent risk factor for the recipient's decreased eGFR at 1-year follow-up.[24]

Renal Parenchymal Fat

The concept of lipid nephrotoxicity was first introduced in 1982[50] and proposed that the initial glomerular injury leads
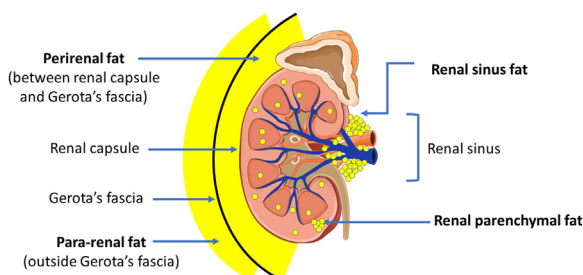

Figure   Anatomy of the ectopic fat around the kidney. Renal sinus fat is the adipose tissue around the renal hilum on the medial aspect of the kidney. The renal capsule is a thin membrane that closely envelops the kidney. The pararenal and perirenal fat are separated by Gerota's fascia (illustrated by a dark demarcation line). The perirenal fat is located between the renal capsule and Gerota's fascia. The pararenal fat surrounds the kidney outside of Gerota's fascia. The renal parenchymal fat is the adipose tissue within the renal cortex and medulla.

to the loss of lipoprotein lipase activator and albumin and causes enhanced hepatic lipoprotein synthesis and hyperlipidemia.[50] In response to filtered lipoproteins, mesangial cells proliferate and produce excess basement membrane materials leading to glomerulosclerosis.[50] This hypothesis was updated in 2009 to include the role of inflammatory stress, endoplasmic reticulum stress, and oxidative stress in renal dysfunction.[51] In response to inflammation accompanied with chronic kidney disease, cholesterol is diverted from the bloodstream to peripheral tissues including the kidney.[51]

With the advancement in renal MRI, renal parenchymal fat could be quantified without the need for renal biopsy. The renal parenchymal fat fraction was significantly higher in type 2 diabetes with microalbuminuria compared with type 2 diabetes without microalbuminuria and non-diabetic control and could be a predictor of early diabetic nephropathy.[11] Individuals in the highest tertile of renal parenchymal fat fraction had a significantly elevated risk for chronic kidney disease compared with those in the lowest tertile, even after adjusting for confounders such as age, BMI, diabetes, and hypertension.[22]

TREATMENT OF FATTY KIDNEY

Lifestyle Interventions

Lifestyle modification is the foundation of chronic disease management and should be encouraged in patients with obesity-related chronic kidney disease. In a review analyzing 6 predominantly lifestyle intervention studies, a hypocaloric diet alone or in conjunction with exercise was commonly successful in reducing weight, blood pressure, and proteinuria while preserving eGFR in a short-term follow-up.[52] In the Look AHEAD (Action for Health in Diabetes) trial, overweight and obese people with type 2 diabetes receiving intensive lifestyle intervention with caloric restriction and exercise had a 31% reduction in the incidence of the very-high-risk category of chronic kidney disease compared with those receiving diabetes support education.[53] Exercise therapy confers cardiometabolic benefits and improves renal function, in addition to weight loss. In the meta-analysis of 13 RCTs, non-dialysis chronic kidney disease patients with exercise therapy had significantly improved eGFR and reduced BMI and blood pressure levels compared with controls.[54]

PHARMACOLOGICAL TREATMENTS

Renin-Angiotensin-Aldosterone System Blockers

The post hoc analysis of the Ramipril Efficacy In Nephropathy (REIN) trial showed the risk reduction for renal disease progression to ESKD and the anti-proteinuric effect of ramipril were more pronounced in obese patients compared with overweight and non-obese patients.[55] The renoprotective effect was greater in obese patients

likely due to the excess of RAAS activation in the obese population.

Mineralocorticoid receptor antagonist (MRA) is also an attractive treatment option. Obesity is associated with leptin-mediated aldosterone excess, which leads to hypertension and endothelial dysfunction, particularly in females.[56] In the FIDELIO-DKD trial, chronic kidney disease patients with type 2 diabetes treated with mineralocorticoid blockade had lower risks of chronic kidney disease progression in the finerenone group compared with the placebo group. The FIND-CKD is an ongoing RCT to evaluate the safety of finerenone in non-diabetic chronic kidney disease patients,[57] and will offer insight into whether finerenone would benefit obesity-related chronic kidney disease patients.

Glucagon-like Peptide 1 Receptor Agonists

Liraglutide and semaglutide are the 2 glucagon-like peptide 1 receptor agonists (GLP-1 RAs) approved for weight loss regardless of diabetes status.[58] Where a minimum of 5% weight reduction from baseline is required to have clinically meaningful effects on metabolic health,[59] a RCT of liraglutide vs placebo showed that 63.2% of patients had at least 5% weight loss and 33.1% had more than 10% weight loss in the study group, compared with 27.1% and 10.6% respectively in the placebo group.[60] In a subsequent RCT of semaglutide vs placebo, 86.4% achieved a weight reduction of 5% or more, 69.1% had 10% or more, and 50.5% had 15% or more compared with 31.5%, 12%, and 4.9%, respectively in the placebo group.[61] Tirzepatide is the newest anti-diabetic medication with dual GLP-1 and glucose-dependent insulinotropic polypeptide properties reported to cause more weight reduction than semaglutide, and is currently under priority review for weight loss indication.[62]

Both liraglutide and semaglutide cause significant reduction in albuminuria and preserve eGFR, with the effects being more pronounced in chronic kidney disease patients.[63] The renoprotective mechanisms of GLP-1 RAs are not well understood, though it is postulated to influence kidneys directly and indirectly. A direct effect is related to natriuresis: GLP-1 RAs inhibit sodium-hydrogen-exchanger-3 at the proximal tubules while stimulate cardiomyocytes to produce atrial natriuretic peptide, thereby increasing distal sodium delivery, inhibiting tubuloglomerular feedback, the RAAS system, and subsequent glomerular hyperfiltration.[64] Additionally, they attenuate ischemic and oxidative stress in the kidneys.[64] The indirect mechanisms are from weight loss and improved glycemic and blood pressure control.[64]

Sodium-Glucose Co-transporter-2 Inhibitors

Sodium-glucose co-transporter-2 inhibitors (SGLT2is) inhibit glucose reabsorption in the proximal tubule, thereby decreasing sodium delivery to the macula densa, leading to tubuloglomerular feedback inhibition, and subsequent afferent arteriolar vasoconstriction and intraglomerular pressure reduction.[65] The CREDENCE, DAPA-CKD, and EMPA-KIDNEY are the 3 main RCTs that provide strong evidence for the renoprotective benefits of SGLT2i in chronic kidney disease patients, extending to those without diabetes.[66-68]

Although SGLT2is are not approved for weight loss indication, they confer 1-3 kgs of weight loss.[69] In the DURATION-8 trial, the weight reduction is enhanced when a SGLT2i is used in combination with a GLP-1 RA, when compared with monotherapies alone.[70]

Anti-obesity Drugs

Other US Food and Drug Administration-approved medications for long-term management of weight loss include orlistat, phentermine-topiramate, and bupropion-naltrexone.[58] These medications do not confer additional renoprotective benefits other than weight loss. Orlistat is a gastrointestinal lipase inhibitor causing fat malabsorption, and has been reported to be associated with hyperoxaluria and oxalate nephropathy.[71-74] Phentermine-topiramate is associated with hyperchloremic non-anion gap metabolic acidosis and serum creatinine elevation; therefore, monitoring of electrolytes, serum bicarbonate, and serum creatinine is recommended before and while on treatment.[75] Bupropion-naltrexone can cause systemic hypertension.[76] Given these adverse effects, they should therefore be avoided or used with caution in chronic kidney disease patients.

Bariatric Surgery

Bariatric surgery is the most effective treatment for severe obesity.[77] Roux-en-Y gastric bypass and vertical sleeve gastrectomy are the most commonly performed procedures, resulting in 20%-30% total body weight reduction.[77] Current indications for bariatric surgery include BMI $\geq$ 35 kg/m^2, regardless of comorbidities, and BMI 30-34.9 kg/m^2 with metabolic disease.[78]

Bariatric surgery confers favorable renal outcomes. Compared with non-surgery patients, bariatric surgery patients had a 58% lower risk for eGFR decline and 57% lower risk of serum creatinine doubling or ESKD.[79] Bariatric surgery also improves chronic kidney disease risk categories defined by the Kidney Disease Improving Global Outcomes consortium criteria where at 1- and 7-year follow-up post-bariatric surgery, the improvements for moderate baseline risk were 63% and 53% respectively, high baseline risk 78% and 56% respectively, and very high baseline risk 59% and 23% respectively.[80] The authors concluded that greater weight loss achieved by bariatric surgery rather than the type of bariatric surgery was an independent predictor of reduced chronic kidney disease risk, and therefore should be sought after as a potential treatment to slow the progression of chronic kidney disease.[80]

In ESKD patients, bariatric surgery was associated with reduced all-cause-mortality at 5 years compared with usual care without surgery.[81] Because obesity is a relative contra-indication for kidney transplantation, bariatric surgery

could be used as a bridge to optimize for kidney transplantation in ESKD patients with obesity.[82]

CONCLUSIONS

Obesity-related kidney disease is expected to be on the rise given the ongoing obesity epidemic. The prevalence of obesity-related glomerulopathy is underestimated because the diagnosis requires a kidney biopsy. Further, the risk of developing this entity may be affected by the presence of APOL-1 risk alleles. On the other hand, ectopic fat accumulation in the kidney can be visualized by non-invasive imaging modalities. Whether "fatty kidney disease" is a distinct disease entity that causes renal damage is not clear. Nonetheless, the treatment principle is the same. Weight reduction should be the utmost priority and can be achieved via lifestyle modification, pharmacological treatments, and bariatric surgery. GLP-1 RA is the preferred class of medication for weight loss over other anti-obesity medications such as orlistat, bupropion-naltrexone, and phentermine-topiramate. GLP1-RAs, when combined with SGLT2is, can confer additive weight loss effect as both attenuate renal hyperfiltration and the RAAS system. Given that adipose tissue has an intrinsic RAAS system, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be considered, especially in the setting of hypertension. MRAs are also a promising option because of leptin-mediated aldosterone production. The FIND-CKD trial would provide further information on whether MRAs can be beneficial for non-diabetic chronic kidney disease patients. Bariatric surgery may soon see a decline in chronic kidney disease progression as another marker of clinical outcome. It is important to tackle the expected rise in "fatty kidneys" with promising new treatment strategies before this entity also becomes an epidemic.

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