REVIEW ARTICLE

The Obese Kidneys

SOURABH SHARMA*, AMANDEEP SINGH†, NITIN KAPOOR‡, SANJAY KALRA#

ABSTRACT

A high incidence of metabolic diseases such as type 2 diabetes mellitus and hypertension, which are well-known as a cause of chronic kidney disease (CKD), is seen in people who are overweight or obese. This has been extensively studied and documented when it comes to how ectopic fat affects different organs for example, the liver. Recently, obesity has also emerged as an independent risk factor for renal disease in individuals with diabetes as well as those without diabetes. When visceral fat accumulates in the kidneys, it causes structural alterations in the kidney along with functional damage leading to the condition referred to as fatty kidney disease (FKD). With this review, we aim to elucidate pathophysiology, diagnostics challenges, and available treatments for the prevention and management of FKD. This knowledge is important for prevention and early diagnosis of CKD, guiding research and improving patient care.

Keywords: Obesity, metabolic syndrome, CaReMe syndrome, fatty kidney disease, obesity-related glomerulopathy, chronic kidney disease

The term "Fatty Kidney", first used by E Richards in 1883, refers to the accumulation of visceral fat within the kidney, leading to various mechanical and physiological changes that result in fatty kidney disease (FKD)[1]. It took a century to recognize that hyperlipidemia is the driving force for lipid accumulation and injury in the kidneys[2]. Numerous studies have unveiled the complex interplay between lipids and kidney disease, especially in the context of obesity, metabolic syndrome, type 2 diabetes mellitus (T2DM), and hypertension[3-8]. While multiple etiologies can lead to kidney enlargement, one of the upcoming and least studied is an obese kidney, or fatty kidney (Table 1).

Ectopic fat deposition refers to the accumulation of excess fat in nonadipose tissues due to insulin resistance or deficiencies in adipose tissue function. As a result, excess energy is stored in organs like the liver, pancreas, kidneys, heart, and skeletal muscles. This visceral adipose tissue (VAT) has significant metabolic implications, with well-known conditions such as nonalcoholic fatty liver disease and nonalcoholic fatty pancreas disease arising from fat deposition in the liver and pancreas, respectively[9,10]. Ectopic fat tends to accumulate in various renal spaces, including perirenal, pararenal, retroperitoneal areas, the renal hilum, and the interstitium. This VAT exerts clinicopathological effects on the kidneys through both mechanical pressure and biochemical disturbances[11-14].

PATHOPHYSIOLOGY OF FKD

FKD is a pathological condition characterized by progressive kidney injury and systemic manifestations such as hyperglycemia and hypertension, which ultimately worsens to kidney failure (Fig. 1).

- **Hyperglycemia:** In T2DM and metabolic syndrome with FKD, triglycerides, and free fatty acids accumulate in the renal cortex, aggravating hyperglycemia through increased gluconeogenesis and decreased glucose utilization[11,12].

  In a healthy state, renal gluconeogenesis accounts for one-fourth of total gluconeogenesis during fasting and half of it in the postprandial state. However, in T2DM and obesity, renal gluconeogenesis is significantly upregulated due to enzymes like phosphoenolpyruvate carboxykinase contributing to hyperglycemia[12,15,16]. Chronic hyperglycemia is also known to promote lipid synthesis and visceral

*Associate Professor, Dept. of Nephrology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India
†Assistant Professor, Dept. of Medicine, All India Institute of Medical Sciences, New Delhi, India
‡Professor, Dept. of Endocrinology, Diabetes and Metabolism, Christian Medical College, Vellore, Tamil Nadu, India; Noncommunicable Disease Unit, Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia
#Treasurer, International Society of Endocrinology (ISE); Vice President, South Asian Obesity Forum (SOF); Bharti Hospital, Karnal, Haryana, India
Address for correspondence
Dr Sourabh Sharma
Room no. 239, Superspeciality Block,
Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India
Email: drsourabh05@gmail.com

Table 1. Etiologies of Enlarged Kidneys

Enlarged kidney	Infiltrative kidney disorder	Acute conditions	Fatty kidney disease/Obese kidneys
• Compensated hypertrophy of solitary functional kidney • ADPKD • HIV nephropathy • Diabetic nephropathy • Renal cancers (Primary/ Metastatic)	• Leukemia • Lymphoma • Amyloidosis • Glycogen storage disease • Xanthogranulomatous pyelonephritis • Granulomatous infiltration • Other chronic infiltrative disorders	• Acute pyelonephritis • Renal abscess • Acute glomerulonephritis • Obstructive nephropathy • Renal vein thrombosis	

ADPKD = Autosomal dominant polycystic kidney disease; HIV = Human immunodeficiency virus.

triglyceride accumulation[17]. On the contrary, excess lipid deposits interfere with glucose utilization, leading to insulin resistance. This interference is due to increased beta-oxidation of free fatty acids and the upregulation of various transcription factors (like carbohydrate-response element-binding protein and sterol regulatory element-binding protein) in response to hyperglycemia. These transcription factors create a vicious cycle of increased lipid accumulation and further impairment of glucose utilization[12,16-20].

- **Hypertension:** FKD predisposes to hypertension through various biomechanical mechanisms. Ectopic kidney fat, particularly that deposited in the renal hilum, compresses renal vasculature and nerve bundles, activating both the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system[7,11]. The raised pressure, which can reach up to 40 mmHg, is directly transmitted to the renal medulla via the renal hilum, which is not covered by the renal capsule and is particularly sensitive to increased intra-abdominal pressures[11,21]. Eventually, there is increased renal tubular sodium reabsorption, and volume expansion, contributing to hypertension. Interestingly, the adipocytes of VAT tend to secrete all RAAS components, further exacerbating hypertension[22].

FKD is still important but a neglected risk factor for chronic kidney disease (CKD). Deposition of ectopic fat in the kidneys leads to mechanical and physiological changes, which progress to CKD[4-7]. The pathophysiology underlying FKD and its conversion into CKD and then end-stage renal disease (ESRD) is described below.

- **Mechanical factors:** The deposition of fat in the renal parenchyma as well as around renal sinus leads to increased renal arterial resistance due to RAAS activation causing tubulointerstitial damage[7,11,12,21]. It causes prolonged decline in glomerular filtration rate, which is a hallmark of CKD.
- **Lipotoxicity:** Tubulointerstitial lipid accumulation plays a pivotal role in kidney injury through a process known as lipotoxicity, characterized by a triad of inflammation, apoptosis, and fibrosis. Fatty acid transporters enable the uptake of lipids, primarily in the form of free fatty acids and triglycerides from circulation. These lipids are stored within various renal cells, including podocytes, mesangial cells, and proximal tubules[12,16,23,24]. Excess free fatty acids in the renal cortex exacerbate insulin resistance by impairing glucose utilization, further contributing to kidney damage[16-20]. Lipotoxicity in tubular cells leads to mitochondrial dysfunction, oxidative stress, and the release of toxic cytokines, ultimately driving the progression of renal fibrogenesis[11].
- **Albuminuria:** Obesity, metabolic syndrome, and T2DM are linked to albuminuria, a key indicator of kidney damage[4-8]. Several epidemiological studies have shown a strong correlation between obesity and the progression of CKD[6]. Obesity-related glomerulopathy (ORG) is a recognized condition that can be considered part of FKD. In ORG, apart from VAT, fat droplets accumulate in the renal parenchyma, particularly in podocytes and interstitium[25,26]. ORG comprises of histological pentad of glomerulomegaly, basement membrane thickening, mesangial matrix deposition, podocyte effacement, and focal glomerulosclerosis[25,26].

  Intrarenal lipid accumulation has already been implicated in the pathogenesis of diabetic nephropathy, hypertensive nephrosclerosis, focal glomerulosclerosis, and various lipid storage disorders[11,12,25]. Podocyte lipotoxicity, which involves impaired insulin signaling, is central to the development of albuminuria in FKD.
- **Hyperleptinemia:** Hyperleptinemia is the key pathogenic mechanism of obesity and plays a significant role in the development of FKD[12]. Renal leptin receptors promote sodium reabsorption,

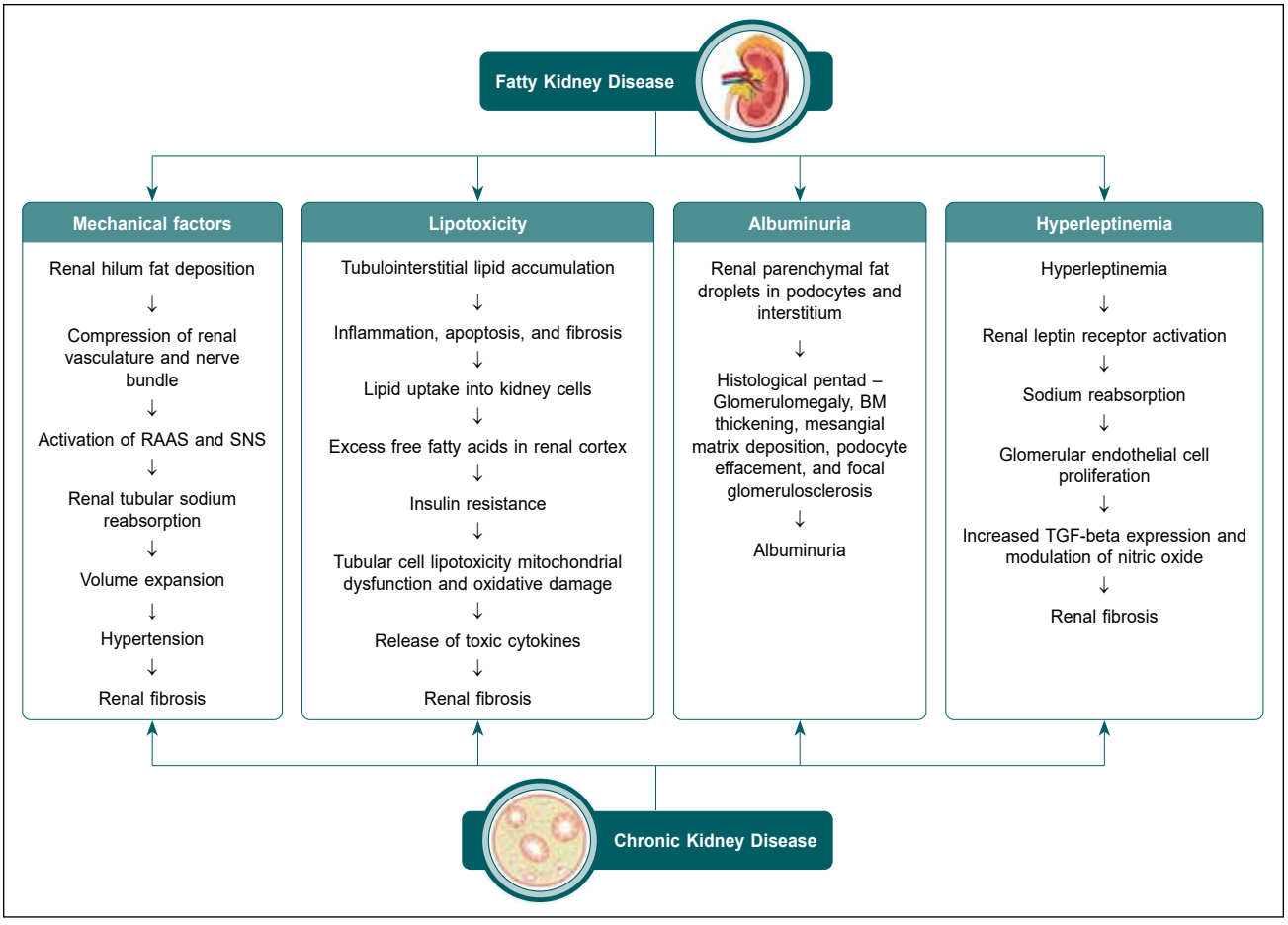

Figure 1. Pathophysiology of fatty kidney disease.

RAAS = Renin-angiotensin-aldosterone system; SNS = Sympathetic nervous system; BM = Basement membrane; TGF = Transforming growth factor.

stimulate glomerular endothelial cell proliferation, and contribute to fibrosis through transforming growth factor (TGF)-beta expression and modulation of nitric oxide and vascular tone. These processes lead to hypertension, focal glomerular sclerosis, albuminuria, and CKD[27-29]. However, interpreting serum leptin levels in CKD can be challenging since the kidneys are responsible for metabolizing leptin[12,27-29].

DIAGNOSIS

Diagnosing FKD is challenging in the outpatient department and usually relies on identifying comorbidities like obesity, metabolic syndrome, and T2DM, along with laboratory parameters such as kidney function tests and urinalysis for albuminuria.

The measurement of renal function in obese patients is challenging due to inaccuracies in estimated glomerular filtration rate (eGFR) equations, which depend on weight and height. López-Martínez et al identified significant errors across 56 serum creatinine or serum cystatin C-based formulas, recommending inulin plasma clearance for precision, although these are impractical for routine use[30]. Early detection of FKD is possible using biomarkers like urinary kidney injury molecule 1, neutrophil gelatinase-associated lipocalin, cystatin C, N-acetyl beta glucosaminidase, podocin, nephrin, podocalyxin, osteopontin, and netrin-1. A urinary proteome classifier, BMI150, has also shown potential in detecting ORG in obese nondiabetic patients, but further validation in large studies is needed.

Radiological investigations such as renal ultrasound and elastography, computed tomography (CT) scans, and magnetic resonance imaging (MRI) are utilized to detect renal ectopic fat, but can only delineate perirenal fat, hilar fat, and renal sinus fat[11,12]. A Doppler ultrasound scan can identify early alterations in vascular flow, while pararenal and perirenal ultrasonographic fat thickness measures visceral fat, showing a stronger correlation with renal dysfunction than traditional anthropometric indicators[31,32]. Ultrasound elastography shows potential

but requires further validation. CT scans offer precise, noninvasive evaluations of kidney structure and fat deposition, while MRI measures fat content without risk of radiation exposure, though it is generally more costly. Renal cortical fat deposits can only be detected by proton magnetic resonance spectroscopy[33,34].

MANAGEMENT

The primary goal in managing FKD is reducing proteinuria, which provides renoprotective benefits. This can be achieved through both nonpharmacological and pharmacological strategies. Nonpharmacological methods include weight reduction through diet and exercise. Pharmacological treatments involve the use of RAAS inhibitors/antagonists, sodium-glucose co-transporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, nonsteroidal mineralocorticoid receptor antagonists, and emerging adjunct therapies. These approaches are crucial in preventing the progression of ORG to ESRD (Fig. 2).

Nonpharmacological management focuses on weight reduction, which significantly lowers proteinuria. A 6%-10% weight loss can reduce proteinuria by up to 70%. Strategies like dietary changes, exercise, and bariatric surgery improve renal function long-term. However, bariatric surgery carries risks, including nephrolithiasis and acute kidney injury. Although weight loss enhances renal outcomes, its benefits are less effective in advanced kidney disease, emphasizing early intervention[35].

In the pharmacological management, RAAS blockade is crucial in managing FKD/ORG, with angiotensin-converting enzyme (ACE) inhibitors and aldosterone antagonists effectively slowing the progression to ESRD. Finerenone, a nonsteroidal mineralocorticoid receptor antagonist, has also shown promising results. SGLT2 inhibitors, beyond glucose control, offer significant renoprotective effects by reducing inflammation, ectopic fat, and proteinuria. Though proven effective in diabetic kidney disease, more studies are needed. GLP-1 receptor agonists also provide renal benefits through weight reduction and anti-inflammatory actions, making them suitable even in CKD and dialysis settings. Combining SGLT2 inhibitors with GLP-1 agonists enhances their protective effects. As these primarily works with weight reduction and other pleiotropic effects, targeted randomized controlled trials are required for definite treatment of FKD[35,36-38].

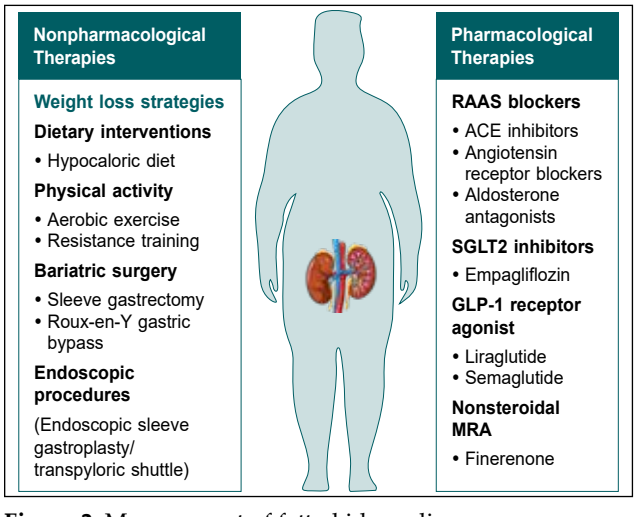

Figure 2. Management of fatty kidney disease.

RAAS = Renin-angiotensin-aldosterone system; ACE = Angiotensin-converting enzyme; SGLT2 = Sodium-glucose co-transporter 2; GLP-1 = Glucagon-like peptide-1; MRA = Mineralocorticoid receptor antagonist.

Bariatric surgery is another viable option, as studies have shown it can normalize glomerular hyperfiltration, improve hypertension, and reduce albuminuria. Long-term research on bariatric surgery has also demonstrated a decrease in CKD incidence[26,39,40].

CONCLUSIONS

Early detection and tailored management strategies are essential in addressing FKD. Advances in biomarkers, imaging, and personalized therapies hold promise for improving outcomes. Timely interventions can slow disease progression, ultimately reducing the risk of CKD and ESRD.

REFERENCES

1. Rickards E. Remarks on the fatty transformation of the kidney. Br Med J. 1883;2(1175):2-3.
2. Moorhead JF, Chan MK, El-Nahas M, Varghese Z. Lipid nephrotoxicity in chronic progressive glomerular and tubulo-interstitial disease. Lancet. 1982;2(8311):1309-11.
3. Fox CS, Larson MG, Leip EP, Culleton B, Wilson PW, Levy D. Predictors of new-onset kidney disease in a community-based population. JAMA. 2004;291(7):844-50.
4. Gelber RP, Kurth T, Kausz AT, Manson JE, Buring JE, Levey AS, et al. Association between body mass index and CKD in apparently healthy men. Am J Kidney Dis. 2005;46(5):871-80.
5. Foster MC, Hwang SJ, Larson MG, Lichtman JH, Parikh NI, Vasan RS, et al. Overweight, obesity, and the development of stage 3 CKD: the Framingham Heart Study. Am J Kidney Dis. 2008;52(1):39-48.
6. Zhang X, Lerman LO. The metabolic syndrome and chronic kidney disease. Transl Res. 2017;183:14-25.
7. Hall ME, do Carmo JM, da Silva AA, Juncos LA, Wang Z, Hall JE. Obesity, hypertension, and chronic kidney disease. Int J Nephrol Renovasc Dis. 2014;7:75-88.

8. Bonner R, Albajrami O, Hudspeth J, Upadhyay A. Diabetic kidney disease. Prim Care. 2020;47(4):645-59.
9. Snel M, Jonker JT, Schoones J, Lamb H, de Roos A, Pijl H, et al. Ectopic fat and insulin resistance: pathophysiology and effect of diet and lifestyle interventions. Int J Endocrinol. 2012;2012:983814.
10. Chen Y, Zhang P, Lv S, Su X, Du Y, Xu C, et al. Ectopic fat deposition and its related abnormalities of lipid metabolism followed by nonalcoholic fatty pancreas. Endosc Ultrasound. 2022;11(5):407-13.
11. Mende C, Einhorn D. Fatty kidney disease: the importance of ectopic fat deposition and the potential value of imaging. J Diabetes. 2022;14(1):73-8.
12. 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(8):854-58.
13. Hti Lar Seng NS, Lohana P, Chandra S, Jim B. The fatty kidney and beyond: a silent epidemic. Am J Med. 2023;136(10):965-74.
14. Verde L, Lucà S, Cernea S, Sulu C, Yumuk VD, Jenssen TG, et al. The fat kidney. Curr Obes Rep. 2023;12(2):86-98.
15. Gerich JE. Role of the kidney in normal glucose homeostasis and in hyperglycaemia of diabetes mellitus: therapeutic implication. Diabet Med. 2010;27(2):136-42.
16. Keane WF. The role of lipids in renal disease: future challenges. Kidney Int Suppl. 2000;75:S27-31.
17. Sun L, Halaihel N, Zhang W, Rogers T, Levi M. Role of sterol regulatory element-binding protein-1 in renal lipid metabolism and glomerulosclerosis in diabetes mellitus. J Biol Chem. 2002;277(21):18919-27.
18. Randle PJ, Garland PB, Hales CN, Newholme EA. The glucose-fatty acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet. 1963;1(7285):785-89.
19. Herman-Edelstein M, Scherzer P, Tobar A, Levi M, Gafter U. Altered renal lipid metabolism in human diabetic nephropathy. J Lipid Res. 2014;55(3):561-72.
20. Whaley-Connell A, Sowers JR. Obesity and kidney disease: from population to basic science and the search for new therapeutic targets. Kidney Int. 2017;92(2):313-23.
21. Sugerman H, Windsor A, Bessos M, Wolfe L. Intra-abdominal pressure, sagittal abdominal diameter, and obesity comorbidity. J Intern Med. 1997;241(1):71-9.
22. Engeli S, Boehnke J, Gorzelniak K, Janke J, Schling P, Bader M, et al. Weight loss and the renin-angiotensin-aldosterone system. Hypertension. 2005;45(3):356-62.
23. Pei K, Gui T, Li C, Zhang Q, Feng H, Li Y, et al. Recent progress on lipid uptake and chronic kidney disease. Biomed Res Int. 2020;2020:3680397.
24. Gai Z, Wang T, Visentin M, Kullak-Ublick GA, Fu X, Wang Z. Lipid accumulation and chronic kidney disease. Nutrients. 2019;11(4):722.
25. de Vries AP, Ruggenenti P, Ruan XZ, Praga M, Cruzdo JM, Bajema IM, et al; ERA-EDTA Working Group Diabesity. Fatty kidney: Emerging role of ectopic lipid in obesity-related renal disease. Lancet Diabetes Endocrinol. 2014;2(5):417-26.
26. D'Agati VD, Chagnac A, de Vries AP, Levi M, Porrini E, Herman-Edelstein M, et al. Obesity-related glomerulopathy: clinical and pathological characteristics and pathogenesis. Nat Rev Nephrol. 2016;12(8):453-71.
27. Kshatriya S, Liu K, Salah A, Szombathy T, Freeman RH, Reams GP, et al. Obesity hypertension: the regulatory role of leptin. Int J Hypertens. 2011;2011:270624.
28. Papafragkaki DK, Tolis G. Obesity and renal disease: a possible role of leptin. Hormones (Athens). 2005;4(2):90-5.
29. Cumin F, Baum HP, Levens N. Leptin is cleared from the circulation primarily by the kidney. Int J Obes Relat Metab Disord. 1996;20(12):1120-6.
30. López-Martínez M, Luis-Lima S, Morales E, Navarro-Díaz M, Negrín-Mena N, Folgueras T, et al. The estimation of GFR and the adjustment for BSA in overweight and obesity: a dreadful combination of two errors. Int J Obes (Lond). 2020;44(5):1129-40.
31. Urban MW, Rule AD, Atwell TD, Chen S. Novel uses of ultrasound to assess kidney mechanical properties. Kidney360. 2021;2(9):1531-9.
32. D'Marco L, Salazar J, Cortez M, Salazar M, Wettel M, Lima-Martinez M, et al. Perirenal fat thickness is associated with metabolic risk factors in patients with chronic kidney disease. Kidney Res Clin Pract. 2019;38(3):365-72.
33. Hammer S, de Vries AP, de Heer P, Bizino MB, Wolterbeek R, Rabelink TJ, et al. Metabolic imaging of human kidney triglyceride content: reproducibility of proton magnetic resonance spectroscopy. PLoS One. 2013;8(4):e62209.
34. Kamba M, Meshitsuka S, Iriguchi N, Koda M, Kimura K, Ogawa T. Measurement of relative fat content by proton magnetic resonance spectroscopy using a clinical imager. J Magn Reson Imaging. 2000;11(3):330-5.
35. Navaneethan SD, Yehnert H, Moustarah F, Schreiber MJ, Schauer PR, Beddhu S. Weight loss interventions in chronic kidney disease: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2009;4(10):1565-74.
36. Martínez-Montoro JI, Morales E, Cornejo-Pareja I, Tinahones FJ, Fernández-García JC. Obesity-related glomerulopathy: current approaches and future perspectives. Obes Rev. 2022;23(7):e13450.
37. Sharma I, Liao Y, Zheng X, Kanwar YS. New pandemic: obesity and associated nephropathy. Front Med (Lausanne). 2021;8:673556.
38. Sharma S, Kalra S. Optimizing finerenone therapy: a comprehensive review using the "Finerenone Pentad". Indian J Clin Pract. 2023;34(7):33-7.
39. Afshinnia F, Wilt TJ, Duval S, Esmaeili A, Ibrahim HN. Weight loss and proteinuria: systematic review of clinical trials and comparative cohorts. Nephrol Dial Transplant. 2010;25(4):1173-83.
40. Chang AR, Chen Y, Still C, Wood GC, Kirchner HL, Lewis M, et al. Bariatric surgery is associated with improvement in kidney outcomes. Kidney Int. 2016;90(1):164-71.