Drug Design, Development and Therapy

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REVIEW

New Perspectives on Obesity-Associated Nephropathy from Pathophysiology to Therapeutics: Revealing the Promise of GLP-1 RA Therapy

Linan Ren[1,2], Feng Ju[3], Siyuan Liu[1,2], Yunjia Cai[1,2], Xiaokun Gang[1], Guixia Wang[1]

[1]Department of Endocrinology and Metabolism, First Hospital of Jilin University, Changchun, Jilin, 130021, People's Republic of China; [2]Institute of Translational Medicine, First Hospital of Jilin University, Changchun, Jilin, 130021, People's Republic of China; [3]Department of Orthopedics, Yuci District People's Hospital, Yuci, Shanxi, 030600, People's Republic of China

Correspondence: Xiaokun Gang; Guixia Wang, Department of Endocrinology and Metabolism, The First Hospital of Jilin University, Changchun, Jilin Province, 130021, People's Republic of China, Email gangxk@jlu.edu.cn; gwang168@jlu.edu.cn

Abstract: Obesity represents a substantial risk factor for a multitude of metabolic disorders, which seriously threatens human life and health. As the global obesity epidemic intensifies, obesity-related nephropathy (ORN) has attracted great attention. ORN arises from both physical/mechanical and non-physical insults to the glomerular and tubular structures precipitated by obesity, culminating in structural impairments and functional aberrations within the kidneys. Physical injury factors include changes in renal hemodynamics, renal compression, and mechanical stretching of podocytes. Non-physical injury factors include overactivation of the RAAS system, insulin resistance, lipotoxicity, inflammation, and dysregulation of bile acid metabolism. Exploring molecules that target modulation of physical or nonphysical injury factors is a potential approach to ORN treatment. ORN is characterized clinically by microproteinuria and pathologically by glomerulomegaly, which is atypical and makes early diagnosis difficult. Investigating early diagnostic markers for ORN thus emerges as a critical direction for future research. Additionally, there is no specific drug for ORN in clinical treatment, which mainly focuses on weight reduction, mitigating proteinuria, and preserving renal function. In our review, we delineate a progressive therapeutic approach involving enhancements in lifestyle, pharmacotherapy, and bariatric surgery. Our emphasis underscores glucagon-like peptide-1 receptor agonists (GLP-1 RAs) as poised to emerge as pivotal therapeutic modalities for ORN in forthcoming clinical avenues.

Keywords: Obesity-related nephropathy, pathophysiology, diagnostics, therapeutics

Introduction

Obesity presents a pervasive challenge to global public health. The combination of unhealthy lifestyles, such as excessive consumption of non-vegetable foods and alcohol abuse, and genetically induced expression of obesity-related genes, such as leptin and melanocortin 4 receptor, may lead to obesity-related diseases.[1,2] From 2005 to 2015, obesity rates in the United States hovered between 30% and 34%, while in the United Kingdom, prevalence ranged from 23% to 24%.[3] The rate of overweight adults in China nearly tripled between 1991 and 2009, increasing from 11.7% to 29.2%.[4] Obesity precipitates the onset of metabolic syndrome and associated comorbidities such as type 2 diabetes (T2DM), nonalcoholic fatty liver disease, hypertension, hyperlipidemia, cardiovascular disorders, obstructive sleep apnea, osteoarthritis, and malignancies, collectively contributing to elevated mortality rates among affected individuals.[5–7]

Chronic kidney disease (CKD) is escalating into a global crisis. In China alone, estimates suggest a staggering 119.5 million individuals affected (ranging from 11.29 to 125 million), translating to an overall prevalence of approximately 10.8% (ranging from 10.2 to 11.3%).[8] Meanwhile, projections indicate that the incidence of end-stage renal disease (ESRD) in the United States could surge from 11% to 18% by 2030. This trajectory, coupled with declining ESRD mortality rates, anticipates a rise in ESRD cases by 29% to 68% over the same period.[9] The rise in CKD incidence appears intertwined with demographic aging and escalating rates of obesity, hypertension, and diabetes. A substantial

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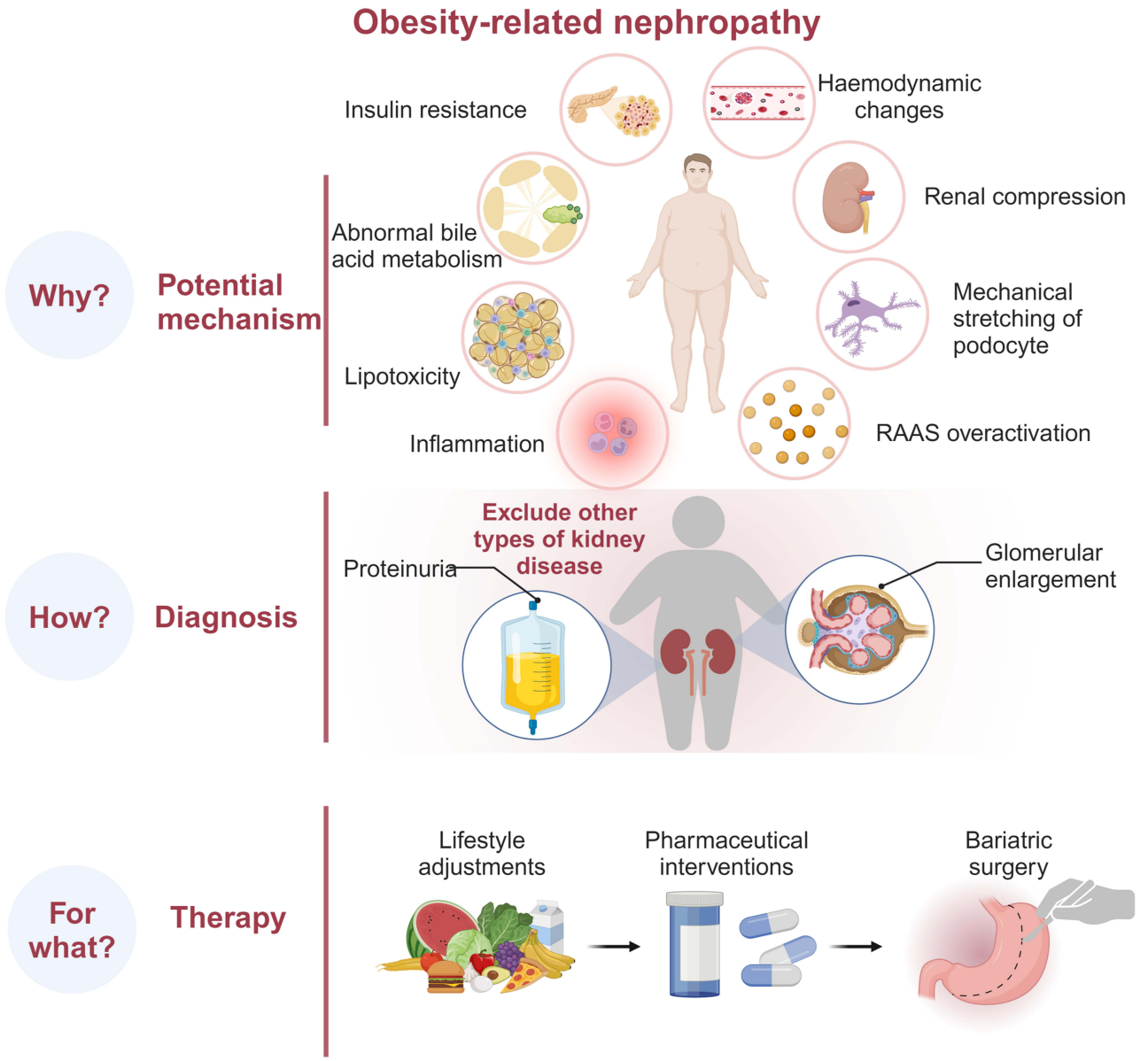
Graphical Abstract



study involving 320,000 participants illuminated the connection between CKD and obesity, demonstrating a progressive elevation in the risk of ESRD with increasing BMI. This relationship persisted even after meticulous adjustments for hypertension, diabetes, smoking history, and cardiovascular conditions among the study cohort.[10] Furthermore, causative links between obesity and CKD were substantiated through a two-sample Mendelian randomization study in European populations.[11] Accumulating evidence underscores the pivotal role of obesity in fostering the progression of CKD.

Kidney involvement caused by obesity alone is known as an obesity-related glomerular disease (ORG), and glomerular enlargement is considered the pathological marker of the disease.[7] However, recent research has revealed that kidney impairment due to obesity extends beyond glomerular damage to include tubular injury as well.[12–15] The disease concept of "obesity-associated proximal tubulopathy (ORT)" was also proposed by Nakamura et al[16]. Therefore, more and more researchers have used the term obesity-related nephropathy (ORN) to describe obesity-induced kidney

injury.[17–19] Kambham et al study showed that the incidence of obesity-related kidney disease diagnosed by kidney biopsy in the United States gradually increased from 0.2% in 1986–1990 to 2.0% in 1996–2000, a 10-fold increase in 15 years.[20] Hu et al analyzed 34,630 biopsy cases of primary kidney disease at Zhengzhou University in China and found that the annual incidence of obesity-related kidney disease increased from 0.86% in 2009 to 1.65% in 2018.[21] However, the actual incidence of ORN is often underestimated due to obesity-related kidney disease, which is often coexisting with metabolic syndromes such as hypertension and diabetes. Moreover, consensus on criteria for diagnosis and treatment with ORN remains elusive. Therefore, a comprehensive grasp of the pathophysiological mechanisms and the latest breakthroughs in diagnosis and treatment of ORN is imperative.

This review consolidates recent strides in elucidating the pathophysiology, diagnosis, and therapeutic strategies for ORN, offering novel perspectives that guide forthcoming research and clinical interventions.

Pathophysiology of ORN

The intrinsic mechanisms of ORN still incompletely articulated, mainly due to the physical/mechanical and nonphysical damage to glomeruli and tubules caused by obesity, which ultimately leads to abnormalities in kidney structure and function (Figure 1).

Physical Injury

Renal Hemodynamic Changes

Glomerular hyperfiltration is an important feature in the early stages of renal impairment in ORG. Renal hemodynamic alterations play a critical role in driving this phenomenon. Recent investigations have identified distinct morphological changes in renal arterioles among ORG patients, notably telangiectasia surrounding glomerular arterioles and vascular

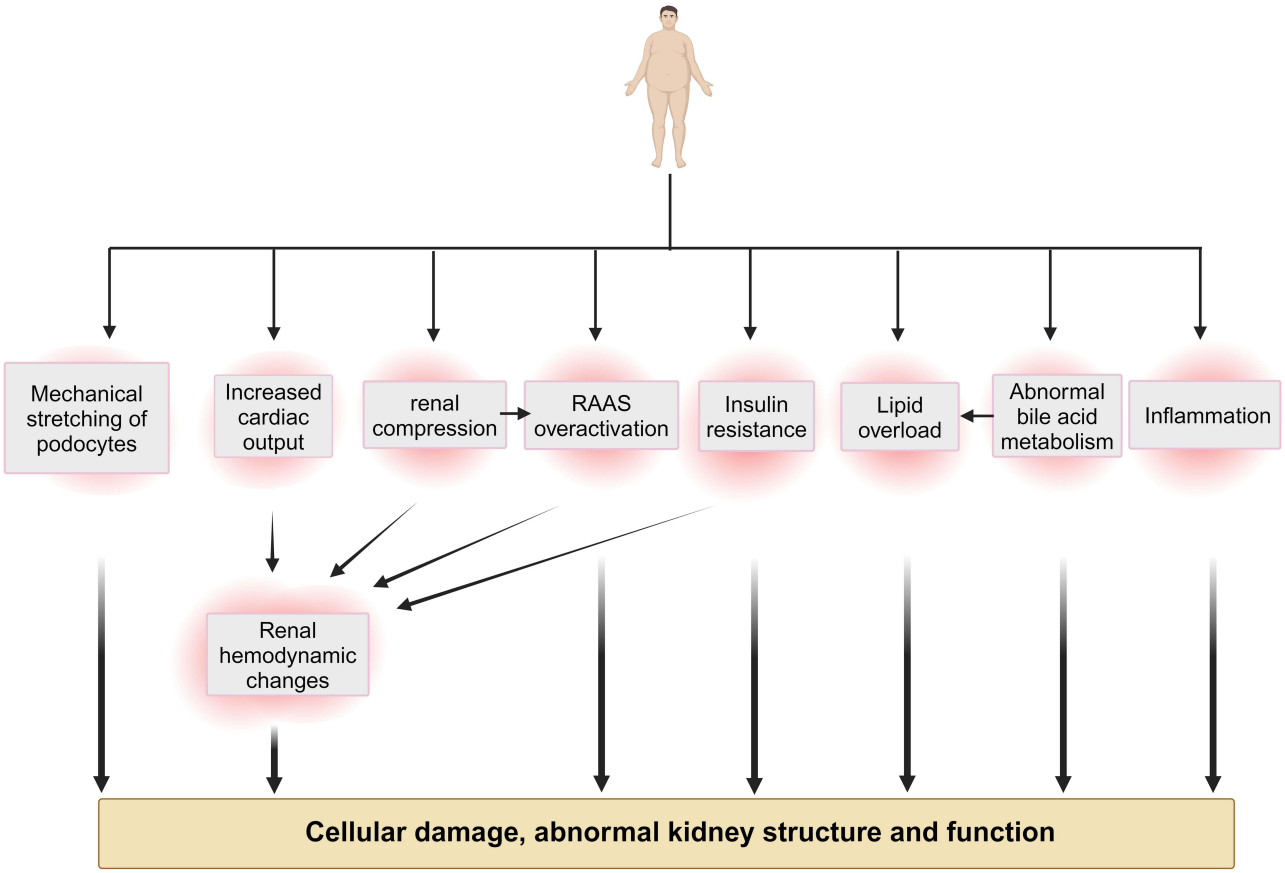


Figure 1 Pathologic mechanisms of ORN.
Abbreviations: ORN, Obesity-related nephropathy; RAAS, Renin-angiotensin-aldosterone system. Created with BioRender.com.

poles, indicative of heightened intravascular flow, local plasma perfusion, and increased pressure.[15] Additionally, Rebelos et al conducted a study comparing renal cortical and medullary hemodynamics in 23 morbidly obese women to 15 age- and sex-matched nonobese controls, revealing significantly elevated total renal blood flow in the obese group compared to controls.[22] Alterations in renal hemodynamics among obese individuals correlate with factors such as heightened cardiac output, activation of the renin-angiotensin-aldosterone system (RAAS), and renal compression, with cardiac output typically increased by approximately 25% in the obese population.[22]

Renal Compression

Renal compression correlates with heightened adipose tissue accumulation and intra-abdominal pressure. Renal compression may result in successive increases in renal blood flow and estimated glomerular filtration rate (eGFR) by decreasing tubular flow velocity, activating the RAAS, decreasing partial excretion of NaCl, and inhibiting tubuloglomerular feedback mechanisms.[23]

Mechanical Stretching of Podocyte

Glomerulomegaly is the mainly histopathologic feature of ORN. Podocytes, as terminally differentiated cells, lack the capacity for self-renewal or differentiation. Therefore, to ameliorate the imbalance between increased glomerular surface area and podocyte proliferation, podocytes are mechanically stretched.[23] In severe lesions, separation of the podocytes from the glomerular basement membrane may occur, leading to focal and segmental glomerulosclerosis.[23]

Non-Physical Injury

Overactivation of the RAAS System

RAAS is a major hormonal cascade response, comprising different angiotensin peptides mediated by different receptors, with several biological functions.[24] In pathophysiological conditions, RAAS is activated to cause vasoconstriction and inflammation, which contributes to hypertension and kidney damage.[25] Overactivation of RAAS in obesity may be related to mechanical hemodynamic changes caused by visceral fat pressing on the renal hilum.[7] Additionally, visceral fat directly syntheses various components of RAAS and neurohormonal stimulation mediated by the sympathetic nervous system, which is affected by hyperleptinemia and insulin resistance, also contributes significantly to the hyperactivation of the RAAS in obesity.[7] Li et al observed a marked elevation in serum Ang II levels in mice subjected to a high-fat diet compared to those in the control group, indicating an association between high-fat diet intake and activation of the renal RAAS system.[26] Elevated Ang II levels disrupt renal hemodynamics by inducing dilation of afferent arterioles, constriction of efferent arterioles, and engaging in both endocrine and paracrine interactions within the renal and systemic RAAS. This cascade, compounded by adipose tissue dysfunction, insulin resistance, and hypertension, culminates in hyperfiltration, glomerular enlargement, and eventual focal glomerulosclerosis.[27] Furthermore, aldosterone has been implicated in promoting kidney inflammation, fibrosis, podocyte injury, and proliferation of mesangial cells.[28]

Insulin Resistance

Insulin resistance represents a crucial hallmark of obesity, with several studies highlighting its potential pathogenic impact on kidney function. Magen et al assessed the relationship between systemic insulin sensitivity and eGFR in a cohort of 1080 overweight and obese children and adolescents. Their findings revealed a significant inverse correlation between insulin sensitivity and eGFR ($B = -2.72$, $p < 0.001$), even following adjustments for confounding variables.[29] Yang et al conducted a longitudinal study spanning 12 years on a prospective cohort of individuals from the general population without CKD, categorizing them into two distinct HOMA-IR trajectories: stable and increased. Their analysis revealed that 8.4% of participants experienced adverse renal outcomes over the study period, with a notably elevated risk observed in the increased HOMA-IR trajectory group compared to the stable group.[30] Insulin resistance exerts a profound impact on renal hemodynamics, triggering glomerular hyperfiltration, endothelial dysfunction, and heightened vascular permeability.[31] During insulin resistance, unbalanced activation of insulin signaling leads to decreased *Akt*-dependent synthesis of the primary vasodilator nitric oxide and enhanced *MAPK*-dependent vascular reactivity. These dysfunctions are implicated in fostering both microvascular and macrovascular abnormalities.[32–34] Abnormal salt

sensitivity likely contributes, at least partially, to the detrimental impact of insulin resistance on glomerular hyperfiltration.[35,36] Additionally, insulin resistance also promotes chronic inflammation of the kidney, apoptosis of renal podocytes and hypertrophy of remaining podocytes.[37,38]

Lipotoxicity

Lipotoxicity refers to a persistent metabolic dysregulation of lipids, resulting in the abnormal accumulation of fat in peripheral organs such as the kidneys, heart, and skeletal muscles. Over time, this process leads to cellular damage and impaired organ function.[39] Several studies have shown renal lipid accumulation in obese individuals.[40,41] The impact of lipid overload in precipitating kidney injury has been extensively documented. Growing evidence suggests that the mechanisms underlying renal cell injury due to lipid overload are intricate and multifaceted, involving inflammation, oxidative stress, endoplasmic reticulum stress, autophagy disorder, and mitochondrial dysfunction.[13,41–43] However, the relationship between lipid accumulation and kidney injury is not unilateral; they may be mutually causal. The heightened activity of the CD36 pathway, pivotal in the uptake of free fatty acids and oxidized low-density lipoproteins, exacerbates lipid-induced toxicity, leading to injury in proximal tubules and podocytes. Conversely, inhibition of CD36 protein expression has shown promise in mitigating renal damage.[44] Consistent with these findings, knockout of *CD36* reversed ectopic renal lipid deposition and prevented kidney damage in obese mice.[45] Thus, dysregulation in lipid metabolism emerges as pivotal in kidney injury. Kang et al observed reduced protein levels of pivotal enzymes governing fatty acid oxidation (FAO) and increased intracellular lipid accumulation in human and murine models exhibiting renal tubulointerstitial fibrosis.[46] In vitro studies have demonstrated that inhibiting FAO in renal tubular epithelial cells results in ATP depletion, cell death, dedifferentiation, and intracellular lipid buildup.[46] These results imply that mitochondrial dysfunction during kidney injury could exacerbate lipid accumulation within renal tissues.

Inflammation

Obesity is distinguished by a state of chronic low-grade systemic inflammation linked to adipose tissue.[47] In physiological states, adipose tissue accumulates around the kidneys and releases adipokines, crucial for regulating immune responses and maintaining vascular homeostasis.[12] However, in obesity, adipose tissue may liberate surplus pro-inflammatory adipokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), while diminishing beneficial adipokines like adiponectin.[12,48,49] Obesity can contribute to renal damage by enhancing the production of pro-inflammatory factors and suppressing the expression of anti-inflammatory factors. A previous study has shown that the synthesis and release of TNF-α and IL-6 may induce programmed inflammation response and exacerbate kidney damage.[50] Increased expression of TNF-α is associated with increased urinary albumin level, renal fibrosis, and glomerulosclerosis in high-fat-fed mice. Conversely, the absence of TNF-α reduced glomerular and tubular damage, and alleviates renal fibrosis.[51] Similarly, blocking IL-6 receptors reduces inflammation levels, immune cell infiltration, and pro-fibrotic cytokine expression in kidney tissue, further reducing kidney damage.[52] In contrast, adiponectin levels are low in obese subjects.[53] Adiponectin is an anti-inflammatory, anti-atherosclerotic, and insulin-sensitizing adipokine.[54,55] Adiponectin stimulates the expression of the anti-inflammatory cytokine, interleukin-10 (IL-10), and reverses the damaging effect of TNF-α, IL-6 and other pro-inflammatory cytokines on the kidneys.[56] Furthermore, adiponectin plays a protective role in podocytes and down-regulates inflammatory and prefibrotic pathways in ORG by stimulating the AMP-activated protein kinase.[7]

Abnormalities of Bile Acid Metabolism

Bile acids perform important signaling functions.[57] In the kidney, bile acids serve as signaling molecules that activate endogenous receptors: the nuclear receptor farnesoid X receptor (FXR) and the membrane-bound G protein-coupled bile acid receptor 1 (GPBAR1, also known as TGR5).[57] Prior research underscores the critical role of bile acids in renal pathophysiology through their activation of FXR, TGR5, and transcription factors pertinent to lipid, cholesterol, and carbohydrate metabolism. Furthermore, bile acids also influence genes involved in inflammation and the development of renal fibrosis.[58] Abnormalities in renal bile acid metabolism in the context of obesity include changes in the bile acid profile and abnormalities in bile acid receptors. Targeted metabolomics analyses by Song et al showed significantly lower levels of chenodeoxycholic acid (CDCA), cholic acid (CA), and lithocholic acid (LCA) in the kidneys of high-fat-fed

rats, suggesting changes in renal bile acid-acid composition in the model of obesity.[59] Reduced FXR expression has also been observed in renal biopsy tissues from patients with ORN.[60] In contrast, altered bile acid metabolic profiles, decreased FXR receptor expression and renal lipid accumulation were reversed after Wen-Shen-Jian-Pi-Hua-Tan decoction treatment.[59] Thus, specific changes in bile acid composition and subsequent activation of FXR in the context of obesity may be key regulatory pathways mediating renal lipid accumulation.

Diagnostics

ORN is characterized by proteinuric nephropathy in individuals with obesity, diagnosed through exclusion of other known renal conditions, utilizing clinical parameters and histopathological assessment.[20,61–64] Glomerular enlargement with or without focal segmental glomerulosclerosis (FSGS) lesions has been detected in kidney biopsy specimens from obesity-related patients. However, these findings lack specificity. Therefore, in the diagnosis of ORN, it is crucial to differentiate from other kidney diseases closely linked with obesity, such as hypertensive nephropathy and diabetic nephropathy (DN). Biopsy specimens from hypertensive obese patients have exhibited moderate to severe vascular lesions, often alongside diffuse collapsed glomeruli. The presence of these histological features typically leads to a diagnosis of hypertensive nephrosclerosis rather than ORN. In obese patients with T2DM, discerning the primary contributor to albuminuria—diabetes or obesity—can pose challenges, particularly during the initial phases of nephropathy. Unlike advanced DN, ORN typically lacks characteristic features such as glomerular nodular degeneration or glomerular microaneurysm formation.[15] Therefore, ongoing pathological investigation into the progression of ORN may offer valuable insights for distinguishing it from DN. Additionally, FSGS is another important histopathological feature of ORG and needs to be distinguished from primary FSGS. Characteristic clinical manifestations of ORG encompass moderate to severe albuminuria, yet without a decline in serum albumin levels.[65] This clinical feature is highly valuable in differentiating these patients from those diagnosed with idiopathic FSGS, with less pronounced foot process effacement observed in ORG patients compared to those with idiopathic FSGS.[20,61]

While albuminuria testing remains widely employed for noninvasive assessment in ORN, it does not always serve as an early indicator of kidney injury.[7] A previous study involving obese individuals undergoing bariatric surgery revealed histological changes consistent with ORG in some patients despite normal renal function and absence of albuminuria.[66] Consequently, recent efforts have focused on identifying new biomarkers for ORN diagnosis. Biomarkers such as urinary kidney injury molecule-1 (KIM-1), urinary cystatin C, urinary N-acetyl-beta-D-glucosaminidase (NAG), and urinary neutrophil gelatinase-associated lipocalin (NGAL) have shown promise in detecting early renal tubular injury in ORG.[67,68] Additionally, ectopic lipid accumulation stands out as a promising new biomarker for assessing kidney injury in ORN patients.[69,70] Renal ultrasound and ultrasound elastography, along with computed tomography (CT) and magnetic resonance imaging (MRI), currently serve as the predominant imaging modalities for evaluating fatty kidneys.[71–77]

In conclusion, kidney tissue biopsy and existing markers of early kidney injury are not specific for the diagnosis of ORN. In the future, it is expected that high-throughput sequencing techniques, such as transcriptomics, metabolomics and proteomics, may facilitate the screening of specific markers of ORN for its early diagnosis and treatment.

Therapeutics

The Role of Lifestyle Modifications in ORN Treatment

The clinical evidence for ORN lifestyle changes comes mainly from observational studies. In a recent randomized controlled trial (RCT) conducted by Straznicky et al, 38 overweight or obese individuals with initially normal kidney function were randomly allocated to groups undergoing dietary restriction, dietary modification combined with aerobic exercise, or receiving no intervention. After a 12-week follow-up, participants in the intervention groups exhibited noteworthy weight reduction, significant decreases in serum creatinine levels, improvements in eGFR, and reductions in albuminuria compared to those in the control group receiving no intervention.[78,79] In a previous study, 63 patients with BMI≥28 kg/m^2 who underwent kidney biopsies and had confirmed ORG were subjected to diet and exercise intervention for 6 months. Among them, 27 patients achieved a substantial reduction in body weight by an average of 8.29 ± 4.00%, accompanied by a 35.3% average decrease in proteinuria. Over the subsequent 24 months, the BMI of these 27 patients decreased further by 9.20 ± 3.78%, with urinary protein excretion showing a marked reduction of 51.33%.[80] This

evidence shows the importance of lifestyle changes in the management of ORN. However, it is important to note that not all dietary interventions are safe and effective for patients with ORN. For example, a very low-calorie ketogenic diet, which mimics fasting, is only safe and effective in obese patients with normal kidney function and mild kidney failure. Because protein is relatively abundant compared to carbohydrates and fats and is generally considered to potentially impair kidney function, it is generally not recommended for subjects with moderate or severe CKD.[81]

ORN Drug Intervention

Anti-Obesity Drugs

The American Gastroenterological Association (AGA) Clinical Practice Guidelines and the Canadian Clinical Practice Guideline strongly advocate for the incorporation of pharmacotherapy alongside lifestyle interventions in adults with obesity (BMI ≥ 30 kg/m², or ≥ 27 kg/m² with obesity-related complications) who exhibit insufficient response to lifestyle measures.[82,83] Therefore, weight loss drug intervention may be the first choice for ORN but not all are suitable for ORN patients owing to be the specific kidney structure and function. The review summarizes the effects of long-term anti-obesity drugs currently approved by the Food and Drug Administration (FDA) on kidney function (Table 1). Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), semaglutide and liraglutide, are highly recommended weight loss agents with renal protective effects.[84] GLP-1 RAs is also a second-line drug recommended by KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease to reduce blood glucose in T2DM and CKD.[85,86] Therefore, semaglutide and liraglutide may be the drugs of choice for the treatment of ORN. Moreover, GLP-1 RAs side effects are relatively small, the most common gastrointestinal reactions such as nausea and vomiting, and the vast majority of patients with symptoms can be alleviated over time.[87,88] Additional research is warranted to ascertain the

Table 1 Effects of Anti-Obesity Drugs on the Kidney

Anti-obesity drug	Study	Subjects	Renal outcome
Semaglutide	Mann JFE et al[94]	Adults with T2DM	Reduce albuminuria; Improve the initial eGFR and then plateau; In patients with moderate to severe renal impairment, the improvement in eGFR was less pronounced compared to those with normal or mildly impaired renal function.
	Shaman AM et al[84]	Adults with T2DM	Lowered albuminuria by 24%; The decline in eGFR slope was notably attenuated by 0.87 mL/min/1.73 m² per year.
Liraglutide	Shaman AM et al[84]	Adults with T2DM	Lowered albuminuria by 24%; The rate of eGFR decline was markedly decelerated by 0.26 mL/min/1.73 m² per year.
	Mann JFE et al[95]	Adults with T2DM	Fewer participants in the liraglutide group experienced renal outcomes.
Phentermine-topiramate ER	Jefferson HJ et al[89]	A case report	Long-term treatment with phentermine resulted in kidney damage.
	Markowitz GS et al[96]	A case report	Treatment with phentermine resulted in acute interstitial nephritis.
	Barnett SM et al[97]	Forty children with epilepsies	80% (4/5) of children had kidney complications due to topiramate.
	Parthvi R et al[90]	A case report	The topiramate-associated renal tubular acidosis was reported.
	Salek T et al[98]	A case report	Metabolic acidosis and kidney stones caused by topiramate.
Naltrexone-bupropion ER	Sauriyal DS et al[99]	Animal experiment	Pretreatment with naltrexone significantly attenuated glycerol-induced rise in plasma creatinine levels.
	Deroee AF et al[100]	Animal experiment	Naltrexone inverts renal function and morphology in cholestatic rats.
	Mutoh J et al[91]	Animal experiment	Naloxone improves kidney function.
	Kinalp C et al[92]	A case report	Kidney damage caused by bupropion.
Orlistat	Erken E et al[93]	A case report	A case with acute kidney injury caused by orlistat.
	Buysschaert B et al[101]	A case report	A case with tubulointerstitial nephritis caused by orlistat.

potential utility of other FDA-approved weight-loss medications in the management of ORN. Evidence on the effects of phentermine-topiramate extended-release (ER) on the kidney is insufficient, but the use of phentermine or topiramate alone reportedly induces kidney disease.[89,90] Similarly, observational evidence on the effects of Naltrexone-Bupropion ER on the kidney remains insufficient. Naltrexone might improve acute kidney injury. Bupropion-induced kidney injury has also been reported.[91,92] Orlistat is a weight loss agent that is not recommended in the AGA clinical practice guidelines for the intervention of obesity in adults.[82] Furthermore, it can cause tubulointerstitial nephritis.[93]

Non-Anti-Obesity Drugs

Drugs for Which There is Sufficient Clinical Evidence.

Sodium-glucose cotransporter 2 inhibitors (SGLT2i)

SGLT2i is a new class of therapeutic hypoglycemic drugs. Although it is not approved as an anti-obesity drug, it plays a role in obesity treatment.[102] SGLT2i can reduce the progression of CKD in patients with obesity and T2DM.[103–108] To assess the effect of canagliflozin on renal outcomes, Perkovic et al enrolled 4401 patients in CKD stages G2 and G3 with T2DM in a randomized double-blind trial. The findings revealed a 34% decrease in the relative risk of renal-specific complications—such as ESRD, doubling of creatinine levels, or death from renal causes—in the canagliflozin group compared to the placebo group.[103] Additionally, in the DAP-CKD trial, the inaugural study of SGLT2 inhibitors to disclose clinical outcomes in non-diabetic chronic kidney disease (CKD) patients, significant reductions in albuminuria were observed across CKD stages G2 to G4, regardless of the presence of type 2 diabetes mellitus (T2DM), and a greater relative reduction in patients with T2DM.[104,108] Consistent with the effect observed in the DAP-CKD trial, Chertow et al also found no evidence of an increased risk of renal outcome in CKD stage G4 patients with dapagliflozin.[109] Moreover, the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease recommends that SGLT2i is the first-line therapy in both T2DM and CKD patients, regardless of glycemic control.[85,86] SGLT2i has not been specifically studied in patients with ORN. SGLT2i could be beneficial in ORN owing to the following factors: Firstly, SGLT2i reduces the reabsorption of sodium and glucose and increases the transport of sodium to the dense macula, induces shrinkage of the afferent arterioles, counteracts glomerular hyperfiltration. Secondly, the weight-reducing effects of SGLT2 inhibitors contribute to the reduction of ectopic renal fat. Lastly, SGLT2 inhibitors mitigate the release of pro-inflammatory cytokines and oxidative stress, thereby ameliorating kidney injury.[110–114]

RAAS Inhibitors.

Given that overactivation of the RAAS system plays a central role in the pathophysiology of ORN, blocking RAAS with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin type II receptor blockers (ARBs) is an effective treatment.[7] Previous Renal Studies showed that losartan reduced the incidence of doubling of serum creatinine levels, albuminuria and ESRD.[115,116] Conversely, Yang et al observed a higher risk of ESRD upon discontinuation of ACEI/ARBs compared with continued use in a prospective population-based cohort study.[117] These observational results suggest that ACEI and ARB therapy can block the progression of CKD and is a potential treatment option for patients with ORN. In addition to ACEI and ARBs, aldosterone secretion has a direct effect on promoting kidney disease. Aldosterone increases TGF-β and PAI-1 levels independently or during interaction with Ang II in the vasculature, which promotes renal vasculature, stiffness and mesangial proliferation, podocyte loss, and development of glomerular fibrosis.[118–122] Morales et al demonstrated that integrating the mineralocorticoid receptor antagonist spironolactone may confer renal advantages in obese patients with albuminuria undergoing ACEI or ARB therapy.[123] However, recent PRIORITY studies have indicated that spironolactone does not halt the progression to microalbuminuria in high-risk patients with T2DM and existing albuminuria.[124] Therefore, additional clinical studies are warranted to elucidate the renal effects of spironolactone in patients with ORN.

Animal Research on Effective Drugs.

TGR5 Agonists. Several drugs have been proven effective in animal experiments for the treatment ORN, but more clinical evidence is needed to prove their effectiveness. G protein-coupled bile acid receptor TGR5 activators are considered promising targets in the treatment of ORN. Previous studies have shown that the selective TGR5 agonist, INT-777, might prevent renal oxidative stress and lipid accumulation by inducing mitochondrial biogenesis.[125] Wang

et al additionally demonstrated that administration of INT-767, a dual agonist of FXR and TGR5, to mice fed a high-fat diet resulted in reduced albuminuria. Moreover, treatment with INT-767 effectively mitigated podocyte injury, mesangial expansion, and tubulointerstitial fibrosis in comparison to untreated control animals.[60]

Melatonin. Melatonin has been reported as a treatment option for ORN.[12] A wealth of studies has elucidated melatonin's antioxidative and anti-inflammatory attributes. Melatonin enhances renal antioxidant enzymatic activities, such as those of glutathione peroxidase (GPX), renal superoxide dismutase (SOD) level, and catalase (CAT), in obese rats with T2DM and Zucker diabetes.[126] Melatonin may prevent and treat systemic inflammatory responses caused by obesity by inhibiting NLRP3 inflammasome activation.[127] Additionally, melatonin may also alleviate obesity.[128] Evidence suggests that supplementation with exogenous melatonin following pinealectomy decreases food consumption, enhances energy dissipation in brown adipose tissue, and diminishes body mass.[129] Thus, melatonin shows promise as a potential treatment for ORN, yet further clinical studies are required to substantiate these findings.

Traditional Chinese Medicine. As a research hotspot in recent years, traditional Chinese medicine may hold promise in the management of ORN. Presently, the efficacy of traditional Chinese medicine in treating ORN is predominantly supported by in vivo and in vitro experiments. Future clinical studies are essential to validate these findings (Table 2).

Effects of Bariatric Surgery on the Kidneys

Surgical intervention may also be an option for patients with ORN. The Canadian Clinical Practice Guidelines for Obesity recommend that bariatric surgery be considered for individuals with BMI ≥ 40 kg/m^2 or BMI ≥35 kg/m^2 with at least one obesity-related disease.[83] Several observational studies have indicated that bariatric surgery-induced weight loss yields favorable effects on renal function within one year post-operatively.[136–140] A meta-analysis revealed that surgical intervention normalized eGFR, lowered blood pressure, and mitigated microalbuminuria in obese patients exhibiting glomerular hyperfiltration.[141] Additionally, to investigate the long-term influence of bariatric surgery on renal function, Iaconelli et al conducted a follow-up study on obese diabetic patients a decade after undergoing biliopancreatic diversion surgery.[142] The research revealed a notable rise in eGFR among surgical recipients (13.6±24.5%) contrasted with a decline in eGFR among those receiving conventional care (−45.7±18.8%). In all patients with baseline microalbuminuria who underwent surgical intervention, microalbuminuria resolved and did not recur, whereas microalbuminuria appeared or progressed to macroalbuminuria in control subjects.[142] These findings suggest that bariatric surgery confers a favorable impact on renal function over both short and extended periods. However, prolonged utilization of bariatric

Table 2 Traditional Chinese Medicines Effective in the Treatment of ORN and Mechanism of Action

Chinese medicine	Study	Mechanism	Renal outcome
Irisin	Han et al[40]	Regulating perirenal adipose tissue function	Reduced urinary albumin excretion, alongside mitigation of renal fibrosis and lipid deposition.
Astragaloside formic acid	Li et al[130]	Alleviating the inflammatory response of perirenal adipose tissue	Improved kidney function
Wen-Shen-Jian-Pi-Hua-Tan	Song et al[59]	Improving renal bile acid composition	Suppressing renal lipogenesis, inflammation, and fibrosis
Curcumin analogue C66	Ye et al[131]	Targeting NF-κB and JNK signaling pathway	Suppressing renal chronic inflammation;
Tabersonine	Qian et al[132]	Inhibited the activation of NF-κB signaling pathway	Enhancement of renal tissue fibrosis mitigation, reduction in renal cell apoptosis, and alleviation of renal tissue inflammation
Sulforaphane	Lu et al[133]	Enhancing autophagy via Nrf2	Reduced body weight, organ-associated fat weight, and urinary albumin/creatinine ratio
Coptidis Rhizoma	Ren et al[134]	inhibited NLRP3 inflammasome complex	Reduced levels of pro-inflammatory cytokines; Reduced glomerular hypertrophy, tethered membrane hyperplasia and loss of podocytes
Magnolia extract	Cui et al[135]	Inhibited inflammation and oxidative stress	Improved kidney damage

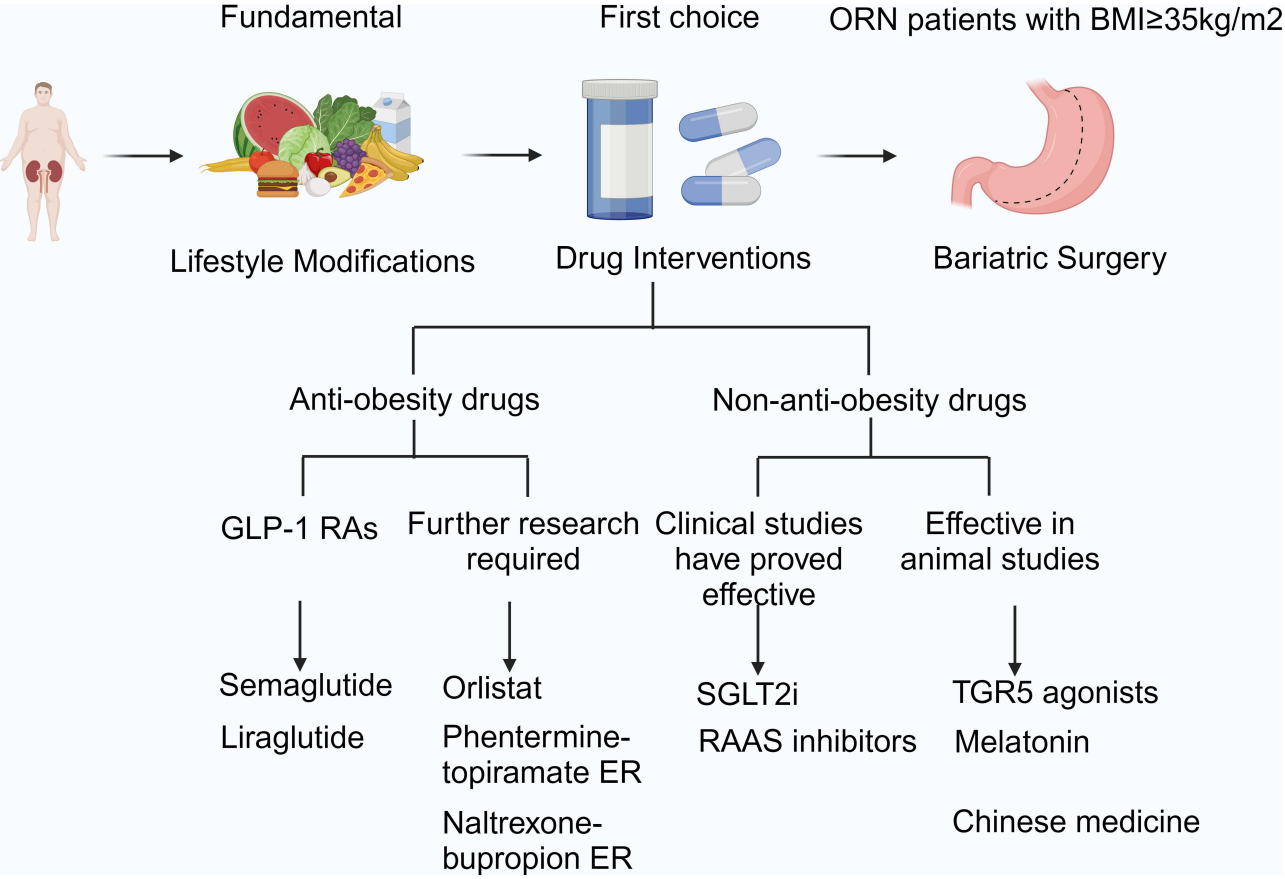


Figure 2 Treatment of ORN.
Abbreviations: ORN, Obesity-related nephropathy; GLP-1RAs, Glucagon-like peptide-1 receptor agonists; Phentermine-topiramate ER, phentermine-topiramate extended-release; Naltrexone-bupropion ER, Naltrexone-bupropion extended-release; TGR5, Takeda G protein-coupled receptor 5; SGLT2i, Sodium-glucose cotransporter 2 inhibitors; RAAS, Renin-angiotensin-aldosterone system. BMI, Body mass index. Created with BioRender.com.

procedures may precipitate additional systemic adversities, notably nutritional deficiency disorders such as metabolic bone disease, secondary hyperparathyroidism, and iron deficiency anemia.[143] Therefore, the indications of bariatric surgery should be fully considered, the advantages and disadvantages should be weighed, and clinicians should pay attention to the postoperative management of patients.

Currently, there is no standardized treatment for ORN. Based on the research evidence described above, we propose a stepwise approach to treatment (Figure 2). Lifestyle changes are the cornerstone. On the basis of lifestyle changes, pharmacologic therapy is given when necessary. GLP-1 RAs such as semaglutide and liraglutide, which are anti-obesity drugs approved by the FDA, are the drug of choice for treatment. The bariatric surgery may be considered if medication is ineffective or for those with severe obesity.

Conclusions

In tandem with the obesity epidemic, the prevalence of ORN is escalating. The intricate pathways driving ORN pathogenesis remain elusive and multifaceted. Mechanisms such as mechanical stress, overactivation of RAAS, insulin resistance, inflammation, lipotoxicity, and dysregulated bile acid metabolism converge to foster renal structural impairment and functional perturbations. The clinical presentations and histopathological features of ORN lack specificity, thus emphasizing the need to exclude alternative renal pathologies. Future advancements aim to discern biological markers of ORN through high-throughput sequencing and comprehensive imaging of high-risk individuals, facilitating early diagnosis. Additionally, there is no standardized method for the treatment of ORN. Lifestyle changes are the foundation

of ORN treatment. GLP-1 RAs such as semaglutide and liraglutide, which are anti-obesity drugs approved by the FDA, may be the drug of choice for treatment.

Abbreviations

ACEI, converting enzyme inhibitors; ARBs, angiotensin type II receptor blockers; DN, diabetic nephropathy; CKD, Chronic kidney disease; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; FAO, Fatty acid oxidation; FSGS, Focal segmental glomerulosclerosis; FXR, Nuclear receptor farnesol X receptor; GLP-1 RAs, Glucagon-like peptide-1 receptor agonists; IL-6, interleukin-6; ORN, Obesity-related nephropathy; ORG, obesity-related glomerular disease; RAAS, Renin-angiotensin-aldosterone system; SGLT2i, Sodium-glucose cotransporter 2 inhibitors; T2DM, Type 2 diabetes; TNF-α, Tumor necrosis factor-α; TGR5, The membrane-bound G protein-coupled bile acid receptor 1.

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