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Review Article

Obesity-Related Glomerulopathy: A Latent Change in Obesity Requiring More Attention

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Keywords
Obesity · Renal disease · Pathology · Ectopic lipid accumulation

Abstract
Background: Obesity has become a major public health problem, and the prevalence of kidney diseases has increased in parallel. Among kidney diseases caused by metabolic disorders, obesity-related glomerulopathy (ORG) is secondary to obesity. ***Summary:*** ORG is mainly caused by glomerular hyperfiltration, dysregulation of hormone and cytokine secretion in adipose tissues, and ectopic lipid accumulation in renal cells. ORG is pathologically characterized by glomerular hypertrophy, with or without focal and segmental glomerulosclerosis. Patients with ORG usually present with proteinuria concomitant with metabolic disorders such as dyslipidemia and hypertension. Weight loss, RAAS inhibitors, and improved insulin resistance can reduce the progression of ORG. ***Conclusion:*** ORG is a growing renal pathological change in obese individuals, and a comprehensive understanding of the disease is pivotal to avoid its occurrence and improve quality of life for those with obesity. ***Key Messages:*** This review comprehensively describes the characteristics of ORG in pathological changes, clinical manifestations, pathogeneses and treatments.

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Introduction

Chronic kidney disease (CKD) has become a severe public health issue, and obesity is one of the risk factors for CKD development and progression [1]. Obesity-driven glomerular hyperfiltration contributes to glomerulomegaly, namely, obesity-related glomerulopathy (ORG), which can lead to the development of proteinuria, secondary focal and segmental glomerulosclerosis (FSGS), and progressive CKD [2]. ORG is defined pathologically as glomerulomegaly, with or without FSGS, occurring in patients with a body mass index (BMI) ≥30 kg/m^2 [3]. Its pathological characteristics include glomerular hypertrophy, FSGS or both, with clinical manifestations of proteinuria and other metabolic disorders. In this review, we described the clinical manifestations, pathology, diagnosis and pathophysiology of ORG. We also summarized the underlying pathogenesis and treatment of ORG.

Clinical Manifestations of ORG

Isolated proteinuria with or without renal dysfunction is the most typical initial symptom in ORG patients [4]. The majority of ORG individuals have subnephrotic proteinuria (<3.5 g/day), and approximately 30% of patients reached nephrotic-range proteinuria [5]. Interestingly, some patients had high levels of proteinuria but no significant decrease in plasma albumin. The mechanisms are not clear, but significantly decreased urinary excretion of N-acetyl-B-glucosaminidase and β_2-microglobulin was observed in those patients [6]. In addition to proteinuria, other symptoms, including hypertension (50–75%) and dyslipidemia (70–80%), also occur in ORG patients [7, 8]. However, the overall manifestations of nephrotic syndrome, especially edema, are rarely presented in ORG patients [5]. Some long-term ORG patients have clinical manifestations of a slow but steady increase in urinary protein, and the proportion of these patients progressing to end-stage renal disease (ESRD) ranges from 10 to 33% [9]. A longer than 2-year follow-up of 20 ORG patients in Japan found that approximately 35% of subjects had a 50% increase in serum creatinine and that 10% developed ESRD [8]. Because of the inapparent clinical features of ORG, the diagnosis is always delayed [2]. Clinicopathological features of glomerulomegaly plus clinical manifestation of obesity and subnephrotic proteinuria are helpful for the accurate and early diagnosis of ORG [4].

Differential diagnoses of ORG include hypertensive nephropathy, diabetic nephropathy, and primary FSGS. Glomerular changes of hypertensive nephropathy are characterized by global glomerulosclerosis and smaller volume than the normal ones, but the remaining nephrons are compensatory hypertrophy [10]. Given the severity of glomerulosclerosis in hypertension-related kidney disease, patients with hypertension as well as obesity whose biopsy results showed moderate-to-severe vascular lesions associated with glomerular degeneration should be diagnosed as hypertensive glomerulosclerosis rather than ORG [10]. The typical pathological changes of diabetic nephropathy are mesangial expansion and glomerular basement membrane thickening, which are distinctive from the mild and always singly occurring "diabetoid" changes in ORG [11]. Moreover, the differences between obesity-related FSGS and primary FSGS were demonstrated in Table 1 [2].

Pathology of ORG

Biopsy and autopsy results showed that the weight and volume of the kidneys in ORG patients were increased when compared to the normal controls [12]. The major microscopic pathological change in ORG is glomerular hypertrophy identified as an increased obesity-related glomerular diameter [13], which occurs as a maladaptation to increased metabolic demands in obesity, but there is no quantitative definition for it [5]. An observation showed that the glomerular volume of ORG patients was approximately three times that of the normal individuals, but the glomerular density was lower [14]. Some patients have a change of FSGS,

Table 1. The differences between obesity-related FSGS and primary FSGS

Obesity-related FSGS	Primary FSGS
Clinical manifestations	
Slowly increasing proteinuria	Sudden proteinuria
Mostly subclinical proteinuria	Mostly nephrotic proteinuria
The absence of nephrotic syndromes (such as the overall performance of nephrotic edema, hypoproteinemia)	Full nephrotic syndromes
Pathological changes	
Glomerular hypertrophy	Normal glomerular volume
Irregular podocyte foot processes loss	Diffuse podocyte foot processes loss

FSGS, focal and segmental glomerulosclerosis.

and among the five subtypes of FSGS, perihilar glomerulosclerosis is the predominant subtype which is attributed to a main load elevation in perihilar vessels in the context of obesity [5]. In addition, some patients were with "diabetoid" changes such as mild focal mesangial sclerosis, mild focal thickening of glomerular basement membranes or tubular basement membranes, but cannot reach the diagnostic criteria for diabetic nephropathy [5]. The electron microscopic structural changes are observed mainly in podocytes with the characteristics of decreases in number and mild foot process fusion [5]. Protein and lipid absorption droplets in glomerular mesangial cells and tubular epithelial cells can also be observed under electron microscopy [15].

Pathogenesis of ORG

Hemodynamic changes, dysregulations of hormone response and abnormal lipid metabolism in the context of obesity are the main pathogenesis of ORG. Hemodynamic changes induced by obesity lead to an increase in multiple parameters such as renal plasma flow (RPF) and glomerular filtration rate (GFR) as well as compensated glomerulomegaly [16]. The renin-angiotensin-aldosterone system (RAAS) interacting with hemodynamic changes in the setting of obesity promotes the progression of ORG [17]. Moreover, dysregulation of hormone response and lipid ectopic accumulation directly or indirectly injure the morphology and function of renal cells, leading to a glomeruli decline and glomerulomegaly [18].

Glomerular Hyperfiltration

Glomerular hyperfiltration is a phenomenon in which glomeruli produce excessive amounts of pro-urine [19], and the mechanism differs among various kidney diseases [16]. In ORG, hypotheses to explain this phenomenon have been proposed: (1) RPF and GFR increase has been observed in the context of obesity, but RPF increases to a lesser extent than GFR, implying the main or sole presence of vasodilation in afferent arterioles (AAs) and subsequent glomerular hyperfiltration [20]. (2) Sodium filtration load increases in proportion to the hemodynamic changes in obesity, and proximal tubules over-reabsorb sodium and water via sodium-glucose cotransporters 1 and 2 (SGLT1 and SGLT2) [21]. The over-reabsorption decreases solute delivery to the macula densa, which decreases tubuloglomerular feedback (TGF) activation and preglomerular vascular resistance, leading to glomerular hyperfiltration [22]. Novikov and Vallon [21] found that SGLT2 inhibition could lower glomerular hyperfiltration independent of blood glucose, implying that proximal over-reabsorption was indis-

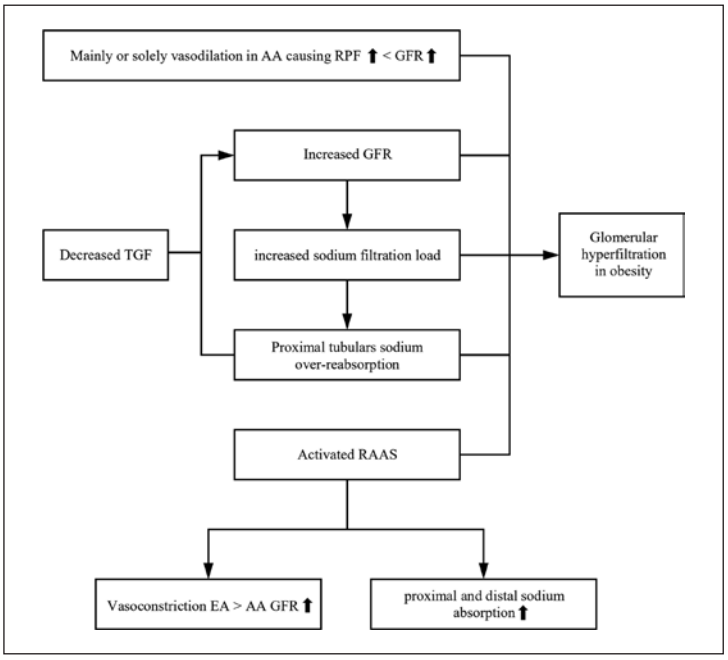

Fig. 1. The mechanisms of glomerular hyperfiltration in ORG. AA, afferent arterioles; RPF, renal plasma flow; GFR, glomerular filtration rate; TGF, tubuloglomerular feedback; RAAS, renin-angiotensin-aldosterone system; EA, efferent arterioles.

pensable in glomerular hyperfiltration [23]. (3) The RAAS or the renin-angiotensin system is a hormone system to regulate blood pressure and fluid homeostasis [24], when RPF is reduced, juxtaglomerular cells convert precursor prorenin into renin and release it into circulation, then, renin is subsequently converted into angiotensin I (Ang I) and angiotensin II (Ang II) by angiotensin-converting enzyme [25]. Adipose tissue can synthesize and secrete all the components of RAAS; thus, the system is overactive in the setting of obesity [26], which increases glomerular hyperfiltration via the following mechanisms. First, Ang II and aldosterone contract vessels, but their effects are greater on efferent arterioles than on AAs, thereby elevating the transcapillary hydraulic pressure difference and GFR [20]. Second, Ang II stimulates luminal Na^+-H^+ exchange and basolateral Na^+-K^+-ATPase to activate the epithelial Na^+ channel and increase proximal and distal sodium absorption [27]. Third, Ang II binds to mineralocorticoid receptors directly, facilitating sodium and water reabsorption [28]. Furthermore, the increased aldosterone in the setting of obesity generates reactive oxygen species which injures podocytes and causes kidney dysfunction [29] (Fig. 1).

Obesity-Induced Dysregulation of Hormone Responses and Lipid Metabolism

Adipokines and Inflammatory Factors

Leptin is a hormone mainly secreted by adipocytes to regulate energy metabolism. The concentration of leptin increases with hyperinsulinemia in the context of obesity, and other factors, such as puberty, female sex, IL-1, TNF-α and corticosteroids also stimulate the leptin secretion [30]. Leptin is mainly cleared by the kidneys; thus, leptin levels increase due to reduced clearance and/or increased synthesis in patients with ESRD, especially when accompanied by factors such as obesity [31]. Hyperleptinemia in obesity plays a role in the pathogenesis of ORG. Leptin promotes the expression of glomerular transforming growth factor-β1 and increases collagen type IV mRNA production, which enhances the accumulation of extracellular matrix and results in renal fibrosis and glomerulosclerosis [32]. Leptin also acts on renal tubules, promoting salt reabsorption and filtration, consequently leading to glomerulosclerosis via TGF-β and subsequent renal dysfunction [33].

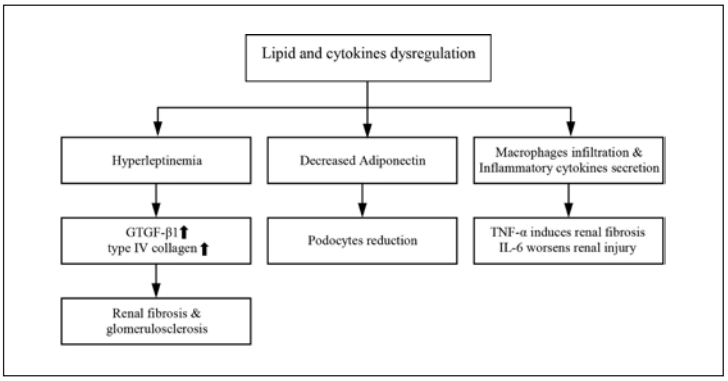

Fig. 2. Hormone and adipokine dysregulation in obesity. GTGF--β1, glomerular transforming growth factor-β1; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6.

Adiponectin maintains podocyte integrity via binding to its type 1 receptor and signaling pathway controlled by 5′AMP-activated protein kinase [34]. Increased BMI reduces adiponectin secretion, leaving the glomerular barrier in a vulnerable condition [35]. Furthermore, excessive caloric intake promotes fetuin-A expression, which attenuates adiponectin production and reduces the activation of energy receptors in liver cells and podocytes, resulting in podocyte reduction and the development of proteinuria [27].

Individuals with obesity have an increased macrophage infiltration in adipose tissues [36]. Interestingly, macrophages and adipocytes interact with each other; for example, fatty acids released by adipocytes stimulate the secretion of TNF-α by macrophages, which in turn increases IL-6 secretion in adipocytes and amplifies inflammation in adipose tissues as well as in the kidneys [37]. TNF-α plays a key role in renal fibrosis progression [38]. Gene analysis found that the expressions of TNF-α and its receptor increased in kidney samples from ORG patients, implying a possible role for TNF-α in the progression of ORG [39]. IL-6 is mainly secreted by adipose tissue systemically and by macrophages locally in the kidney [40]; glomeruli from ORG individuals exhibited increased expressions of IL-6 transducer, suggesting IL-6 may be a risk factor for renal injury in obesity [41].

Connexin43 (Cx43) is a component protein of gap junctions between podocytes which is strongly expressed by immunocytes [42]. Cx43 promotes monocyte adhesion in the endothelium and activates profibrotic pathways in tubular and interstitial cells in the context of kidney diseases [43]. The results of a study on ORG rat models showed that the expression of Cx43 was significantly upregulated when compared with the controls, and the overexpression of Cx43 in patients with obesity was associated with renal inflammation, implying that Cx43 may be a potential target protein for ORG progression [44] (Fig. 2).

Nephrotoxicity of Ectopic Lipid Accumulation

Obesity aggravates intracellular lipid accumulation, and the nephrotoxicity of ectopic lipid accumulation was proposed by Moorhead in 1982 with the statement that hyperlipidemia led to glomerulosclerosis via intracellular lipid accumulation in injured kidneys [45, 46]. The mechanisms differ among cell types owing to their specific characteristics.

Mesangial Cell Foam Cell Formation-Induced Glomerular Hypertrophy. Owing to the absence of a basal membrane between the glomerular endothelium and mesangium, mesangial cells directly contact lipoproteins [15]. Endothelial dysfunction has been found in obesity, which results in lipoprotein leakage; besides, mesangial cells engulf various kinds of lipids via the housekeeping and phagocytic functions. Mesangial cells accumulate cholesteryl esters via LDL receptors, modified LDL and long-chain fatty acids via scavenger receptors [47]. They express apolipoprotein B and E (apoB and apoE) and accumulate triglycerides via lipoprotein lipase [48, 49]. In addition, inflammation disrupts LDL receptor feedback, causing unopposed

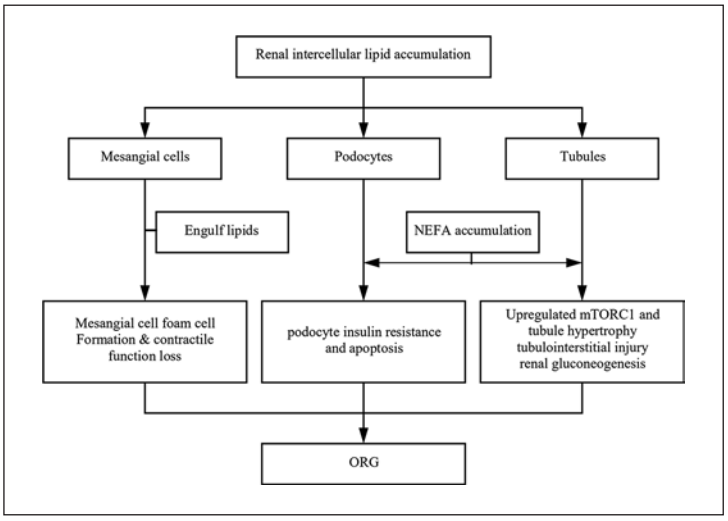

Fig. 3. Renal intercellular ectopic lipid accumulation. mTORC1, mammalian target of rapamycin complex 1; NEFA, non-esterified fatty acid; ORG, obesity-related glomerulopathy.

lipid accumulation [50]. By these mechanisms, excessive lipid is aggregated in mesangial cells and consequently results in cellular foam formulation and contractile function loss, leading to diminished structural integrity of capillary loops and glomerulomegaly [15].

Podocyte Loss and Kidney Dysfunction. Patients with ORG exhibited approximately 45% podocyte loss [51]. Podocyte loss is irreversible because they are terminally differentiated cells and incapable of self-renewal or differentiation [52]. Moreover, podocyte loss is believed to trigger further loss because their partial deficiency induces adaptive hypertrophy in the remaining podocytes to meet the increased mechanical strain, but the adaptation seems to be insufficient, thus causes secondary or adaptive focal segmental glomerulosclerosis [53].

Insulin is critical for podocyte survival because insulin signaling regulates podocyte morphology adaptations to postprandial changes in intracapillary pressure and GFR [54]. In metabolically unhealthy obesity, NEFA accumulation in podocytes is related to podocyte insulin resistance and apoptosis [55]. Cholesteryl ester and fatty acid accumulation interfering with insulin signaling leads to podocyte-specific insulin resistance, loss of podocyte compliance with postprandial changes in GFR, podocyte apoptosis, and a subsequent thwarted hypertrophy of the remaining podocytes and the development of glomerulosclerosis [15].

Tubules Absorb NEFA-Enveloped Proteins, Contributing to Renal Gluconeogenesis. The proximal tubules become hypertrophic to match hemodynamic and metabolic load changes caused by the increased sodium, water and albumin absorption in the setting of obesity [56]. Patients with obesity, presenting proteinuria, over-expressed mammalian target of rapamycin complex 1 (mTORC1) in PT cells, which is associated with growth and lipogenesis and may be indispensable to proximal tubule hypertrophy and lipid accumulation [57]. NEFA absorption in renal tubular tissue increases proportionally with plasma NEFA levels and glomerular albuminuria elevation in obesity [58]. Experimental studies indicated that excessive NEFA load in proteinuria-induced tubulointerstitial injury was correlated with a diminished autophagy response [57]. Moreover, NEFAs accumulated in proximal tubules undergo oxidation to produce ATP for the highly energetic transport processes [58], but the majority of NEFAs are incorporated into lipid droplets as triacylglycerol [59]. The abundance of triacylglycerol accumulation in the proximal tubules drives renal gluconeogenesis through increased acetyl-CoA concentrations [60], which prevents insulin's suppressive effect on gluconeogenesis. Lipid ectopic accumulation, together with upregulated mTORC1, interferes with tubular insulin signaling, leading to the enhanced renal gluconeogenesis and eventually to increased tubular atrophy and interstitial fibrosis [15] (Fig. 3).

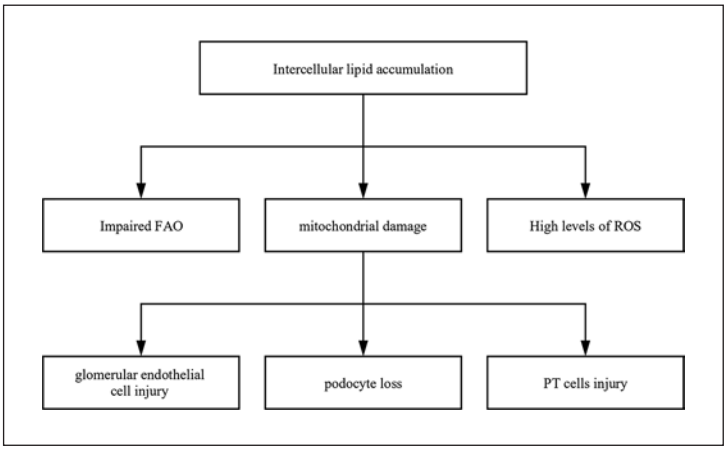

Fig. 4. Mitochondrial dysfunction in renal cells. FAO, fatty acid β-oxidation; ROS, reactive oxygen species; PT, proximal tubules.

Mitochondrial Dysfunction. Intercellular lipid accumulation in renal tissue alters mitochondrial structure and function mainly via impaired fatty acid β-oxidation and excessive reactive oxygen species production, which in turn impairs normal renal cell function and leads to kidney disease progression [61]. Mitochondrial damage triggered by excess lipids accumulation appears in all renal cell types, presenting as size reduction, cristae membrane loss, and matrix density decrease [23]. The effects of mitochondrial dysfunction in the kidneys are also cell-type specific. For example, mitochondrial dysfunction induced glomerular endothelial cell injury and approximately 50% cell loss in mice after 28 weeks' high-fat diet (HFD) intervention [62]. Besides, in mice fed a HFD, significant dilation of ER lumen, an indication of ER stress, was observed in podocytes, causing pronounced cell loss; and the surviving podocytes exhibit deformed and flattened foot processes owing to the actin cytoskeleton damage caused by ATP deficiency during actin assembly. Those changes of podocytes lead to proteinuria and glomerulosclerosis [63]. Furthermore, mitochondrial damage is associated with excessive accumulation of lipid droplets, autophagic vesicles, and myelin figures in PT cells [23] (Fig. 4).

Treatments for ORG

Factors Predisposing to ORG

There are factors other than obesity affecting the prognosis of ORG, including obesity type, metabolic syndrome, obesity-related syndrome or complications, low nephron number, reduced nephron mass and renal dysfunction caused by other diseases.

Obesity Types

Obesity type is categorized into visceral fat deposition and subcutaneous fat deposition. People with visceral fat deposition, especially those with morbid obesity (MO), have a higher risk of albuminuria and ORG [64].

Metabolic Syndrome

Individuals with obesity and metabolic disorders, such as impaired glucose tolerance, hypertension and dyslipidemia, are more prone to developing glomerulopathy [65]. A recent study showed that there are no obvious differences in the incidence of CKD between metabolically normal obese and lean people, but a higher CKD incidence could be observed in indi-

viduals with metabolically abnormal obesity when compared with those with normal BMI, implying that obesity combined with metabolic disorders may increase the risk of kidney injury [66].

Obesity-Related Syndromes or Complications

Individuals with obesity-related syndromes or complications such as sleep apnea, pulmonary hypertension, right ventricular overload and nonalcoholic fatty liver disease (NAFLD) are more likely to develop ORG [67]. Individuals with sleep apnea and nocturnal hypoxemia always exhibit pulmonary hypertension and right ventricular overload, which increases renal vein pressure and activates the RAAS system, resulting in renal injury [68]. A cohort study of 1,525 CKD patients showed that the decline in eGFR was greater in those with higher NAFLD fibrosis scores, indicating that NAFLD may accelerate renal failure in patients with CKD [69].

Decreased Nephron Mass

Patients with congenital kidney anomalies and ureter dysplasia or nephrectomies have decreased nephron mass. The mismatch between body and kidney size caused by obesity further contributes to the decline in nephron mass, leading to a vicious cycle of glomerular failure and injury [70, 71].

Number of Nephron Units

The number of nephron units is determined at birth. Low birth weight, premature birth, and abnormal kidney development may result in a decrease in nephron number. In addition, the number of podocytes is also congenitally determined, and they are unevenly distributed in nephrons. A low number of podocytes attenuates the adaptability to glomerular hypertrophy in patients with obesity and leads to renal pathological changes [72, 73].

Chronic Kidney Disease

Increased obesity-related hemodynamics and metabolic burden in individuals with obesity aggravates CKD that has already developed [74]; thus, those with CKD tend to develop ORG.

Treatments for ORG

Weight Loss

Urinary protein reduction is notable in patients with ORG after weight loss, which can be achieved via low-calorie diets or bariatric surgery. The effects of bariatric surgery on patients with MO were overt. A long-term prospective follow-up (76 ± 42 months) conducted on 92 MO subjects who were with normal renal function or mild pathological ORG changes and had undergone bariatric surgery observed drastic weight loss as well as significant blood pressure decrease in these individuals. Creatinine clearance increased slightly in the first 5 years, decreased significantly during the following 2 years then kept stable. Although no apparent changes were observed in serum creatinine, albumin levels or the number of glomerular lesions, the weight loss surgery was proven effective to maintain normal renal function in the short-term and long-term, and alleviate hypertension and proteinuria in MO patients [75]. Notwithstanding, some studies pointed out that the incidence of renal failure after weight loss surgery was significantly increased in MO patients with CKD; thereby, further evaluation of the surgery is warranted [33].

RAAS Inhibitors

RAAS inhibitors have been proven efficient among patients with proteinuria, especially for those with obesity [76]. Mallamaci et al. [77] found that the antiproteinuric effects of

ramipril in individuals with obesity were greater than those with overweight and normal BMI (reductions of 86, 45, and 42%, respectively), suggesting that individuals with obesity were more sensitive to RAAS blockers. Moreover, a long-term follow-up study noted that the anti-proteinuric effects of RAAS blockers were attenuated over time, especially in those without any weight loss or even with weight gain [77].

Hypoglycemic Drugs in ORG Treatment

Incretin-based therapy such as dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists (vildagliptin or liraglutide) inhibited ORG development in HFD-induced ORG mouse models, partly by increasing systemic insulin sensitivity and suppressing local inflammation and podocyte autophagy, mainly by reducing monocyte and M1 macrophage infiltration and TNF-α and IL-6 productions [78, 79]. Data from experimental models of kidney disease demonstrated that metformin may be potentially therapeutic for ORG due to its antifibrotic effects [80].

Treatment for Lipid Metabolism Regulation

Abnormal lipid metabolism plays a pivotal role in the occurrence and development of renal lipid ectopic accumulation, inflammation, oxidative stress, and renal fibrosis. Novel treatments for lipid dysregulation are promising therapeutic agents for ORG. Wang et al. [81] found INT-777, the selective agonist of G protein-coupled bile acid receptor TGR5, could decrease proteinuria, podocyte injury, mesangial expansion, fibrosis, and macrophage infiltration in the kidneys of diabetic db/db mice. Besides, it induced mitochondrial biogenesis and suppressed renal oxidative stress as well as lipid accumulation, preventing kidney diseases in mice with diet-induced obesity [81]. Lipoxin A4, an important down-regulator of IL-12 production, was proven to be effective in attenuating the renal inflammatory response and injury in the ORG mouse model via suppressing the activation of NF-κB and ERK/p38 mitogen-activated protein kinase (MAPK) pathways. Thereby, it may also be potentially therapeutic for ORG [82].

Novel Treatments

SS-31, a mitochondria-targeting antioxidant, protects glomerular endothelial cells and podocytes, inhibits the upregulation of mesangial expansion, glomerular sclerosis, macrophage infiltration and inflammatory factors (including TNF-α, MCP-1, and TGF-β) as well as prevents mitochondria from lipotoxicity, making it a novel upstream drug for the treatment of ORG [23]. Zinc downregulates P38 MAPK-mediated inflammatory responses and slows down the progression of ORG [83]. Curcumin reduces the leptin toxicity on podocytes by inhibiting the Wnt/β-catenin signaling pathway, which can be regarded as a potential treatment for ORG [84]. mTOR inhibitors are effective to reduce fat accumulation in the kidneys [15], and the selective endothelin A receptor antagonists can reduce proteinuria and preserve renal function in diabetic patients [85]; thus, these drugs may be potential treatments for ORG patients. A high-fiber diet and fecal probiotic transplantation suppresses inflammation in ORG patients by promoting healthy probiotic growth, which is promising for ORG treatment [32]. Moreover, an early alanine-rich dietary intervention is another option for attenuating ORG progression [83].

Conclusions and Future Directions

ORG is a pathological change characterized by glomerulomegaly, FSGS, or both occurring in patients with BMI ≥30 kg/m^2. Patients have clinical manifestations of subnephrotic proteinuria and an absence of overall symptoms in nephrotic syndrome. Hemodynamic

changes, dysregulation in lipid metabolism and hormone responses in the setting of obesity are the main etiology of ORG. Weight loss and RAAS inhibitors are effective treatments for ORG, and other medications such as anti-hyperglycemia medications, lipid metabolism regulators and other novel treatments are alternative and promising possibilities.

There are some questions that require further exploration. Which new metabolic pathways, activation factors, and pathological mechanisms can regulate ectopic lipid accumulation? The early clinical diagnosis of ORG is still hard to achieve owing to lack of ideal early-onset clinical biomarkers. Proton magnetic resonance spectroscopy assessment of fat content in tissues has its limitations, whereas noninvasive MRI may have greater application value, but more data are warranted to evaluate its efficiency [15]. Moreover, the effectiveness and feasibility of bariatric surgery for ORG patients require further evaluation [2]. With the growing prevalence of ORG nowadays, the studies on ORG have achieved promising prospect, and we believe the pendent problems will be solved in the near future.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.Y. wrote the manuscript. C.C. and T.D. revised the manuscript. Z.Z. provided the idea and reviewed the manuscript.

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