Front. Med. 2017, 11(3): 340–348
DOI 10.1007/s11684-017-0570-3

REVIEW

Obesity-related glomerulopathy: pathogenesis, pathologic, clinical characteristics and treatment

Tianhua Xu, Zitong Sheng, Li Yao (✉)

Department of Nephrology, The First Hospital of China Medical University, Shenyang 110001, China

Abstract **In light of the rapid increase in the number of obesity incidences worldwide, obesity has become an independent risk factor for chronic kidney disease. Obesity-related glomerulopathy (ORG) is characterized by glomerulomegaly in the presence or absence of focal and segmental glomerulosclerosis lesions. IgM and complement 3 (C3) nonspecifically deposit in lesions without immune-complex-type deposits during ORG immunofluorescence. ORG-associated glomerulomegaly and focal and segmental glomerulosclerosis can superimpose on other renal pathologies. The mechanisms under ORG are complex, especially hemodynamic changes, inflammation, oxidative stress, apoptosis, and reduced functioning nephrons. These mechanisms synergize with obesity to induce end-stage renal disease. A slow increase of subnephrotic proteinuria (< 3.5 g/d) is the most common clinical manifestation of ORG. Several treatment methods for ORG have been developed. Of these methods, renin–angiotensin–aldosterone system blockade and weight loss are proven effective. Targeting mitochondria may offer a novel strategy for ORG therapy. Nevertheless, more research is needed to further understand ORG.**

Keywords obesity-related glomerulopathy; pathogenesis; pathologic; clinical characteristics

Introduction

The obesity epidemic has led to an increase in the number of incidences of obesity-related glomerulopathy (ORG), which is pathologically defined as the occurrence of glomerulomegaly and focal and segmental glomerulosclerosis (FSGS) in patients with BMI of $\geqslant$ 30 kg/m^2. ORG has become a global issue, and its prevalence has increased substantially [1]. A clinicopathological study of native renal biopsies showed that a progressive increase in incidence of biopsy proved ORG from 0.2% in 1986–1990 to 2.0% in 1996–2000 ($P = 0.0001$) and further to 2.7% in 2001–2015 [2,3]. This worldwide obesity epidemic has brought immense medical concern. Obesity is an important and independent risk factor for chronic kidney disease (CKD). The mechanisms involved in ORG are complicated and integrated, especially hemodynamic changes, inflammation, oxidative stress, and apoptosis. Nephrotic proteinuria (> 3.5 g/d) is occasionally present, but typical nephrotic syndrome is characteristically absent. Furthermore, about 30% of ORG patients develop progressive renal failure or end-stage renal disease (ESRD). Hypertension and dyslipidaemia are also commonly observed in ORG patients. In this article, we review the clinical and pathological characteristics, pathogenesis, and treatment of ORG.

Received January 14, 2017; accepted July 19, 2017
Correspondence: liyao_cmu@163.com

Pathology characters of ORG

ORG is characterized by glomerulomegaly in the presence or absence of FSGS lesions (Fig. 1) [2,4,5]. Glomerulomegaly is identified through measuring the diameters of all glomerulus samples or those sectioned through the hilus, which is in the central part of the glomerular globe [3]. In other methods, the serial sections of an individual glomerulus are used to estimate glomerular volume [6]. In a Columbian study, the glomerular diameter in ORG (mean 226 μm) significantly increased to a greater extent in comparison with those in age- and sex-matched normal controls (mean 168 μm; $P < 0.001$) [2]. Glomerulomegaly is accompanied by mesangial proliferation, matrix accumulation, and hypertrophied podocytes with milder foot process fusion [7].

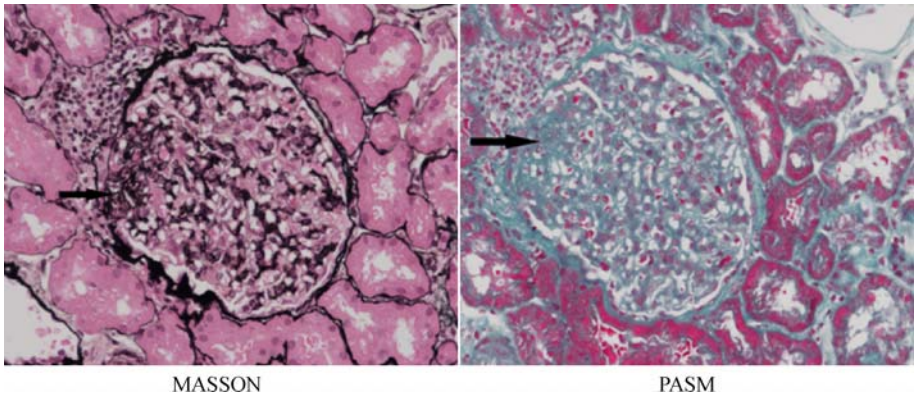

Fig. 1 Glomeruli of patients with ORG. Glomerulomegaly is present, and increased capillaries number is observed. Capsular space is restricted, and segmental sclerosis sites are located near the vascular pole (magnification 200×).

FSGS is defined as a segmental consolidation of the glomerular tuft by extracellular matrix and/or hyaline, resulting in capillary obliteration [4]. FSGS lesions are predominantly perihilar and typically observed in hypertrophied glomeruli [8]. Perihilar lesions might also contain other glomerular globe parts. Exclusively perihilar lesions are observed in 19% of ORG biopsy samples, and a mixture of perihilar and peripheral lesions in 81% [2]. This observation indicates that the ultrafiltration pressure at the afferent end of the glomerular capillary bed is greater than that at the efferent end, and this difference in ultrafiltration pressure leads to afferent arteriole reflex dilation [9]. In contrast to primary FSGS, which shows diffuse effacement, ORG-related FSGS presents an irregular mild foot process effacement under an electron microscope. Furthermore, the experimental models of ORG showed that glomerular tuft volume increases exponentially in relation to body weight gain in wild-type Fischer intact rats kept on an *ad libitum* diet [10]. The numerical density of podocyte decreases as the renal mass and glomerular diameter increase, thereby inducing the extension of podocytic processes and covering the expanded area. This expansion can cause podocyte detachment, which induces loss in protein selectivity and formation of denuded areas. The loss of protein selectivity and presence of denuded areas trigger matrix deposition and inflict podocyte injury, finally causing glomerulosclerosis [11,12].

In addition, lipids are deposited in mesangial cells, podocytes, and proximal tubular epithelial cells [13]. The loaded lipids in the mesangial cells induce structural damage and function loss. Lipid deposition in podocytes leads to insulin resistance and apoptosis, while accumulation of nonesterified fatty acid (NEFA)-bound albumin causes atrophy and interstitial fibrosis in tubular cells [14]. "Diabetoid" changes (focal mesangial sclerosis, focal thickening of glomerular and tubular basement membranes) in glomeruli are frequently observed in obese patients without diabetes [2,4], indicating shared molecular pathways in diabetic glomerulosclerosis and ORG [15]. In ORG-related FSGS, tubular atrophy and interstitial fibrosis are typically mild (mean 1.26 +) similar to interstitial inflammation (mean 0.8 +). Arteriolosclerosis ranges from mild to moderate (mean 1.42 +) [2] and is generally milder than primary FSGS.

In ORG biopsy samples, nonspecific deposition of IgM and C3 in the lesions of sclerosis and hyalinosis can be detected through immunofluorescence. No other immune-complex-type deposit is present. ORG can also superimpose on other renal diseases, such as IgA nephropathy [16].

Clinically significant obesity is the leading cause of ORG. However, many studies confirmed that mild renal pathological alterations are observed in a large number of patients with morbid obesity but without clinical evidence of renal disease [17]. Thus, future research must focus on determining whether renal biopsies must be considered in patients with mild obesity for the detection of any presence of subclinical renal injury similar to that observed in extremely obese patients.

Mechanisms of ORG

The mechanisms involved in ORG are complex. Adipose tissue is unbalanced in terms of lipid accumulation in renal cells, and the effects of obesity-associated diseases, such as hypertension, diabetes, dyslipidemia, insulin resistance, and obstructive sleep apnea (OSA), contribute to ORG occurrence. ORG primarily contributes to renal injury through multiple effectors, adipokines, lipids, renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), inflammation, oxidative stress, and apoptosis (Fig.2) [18].

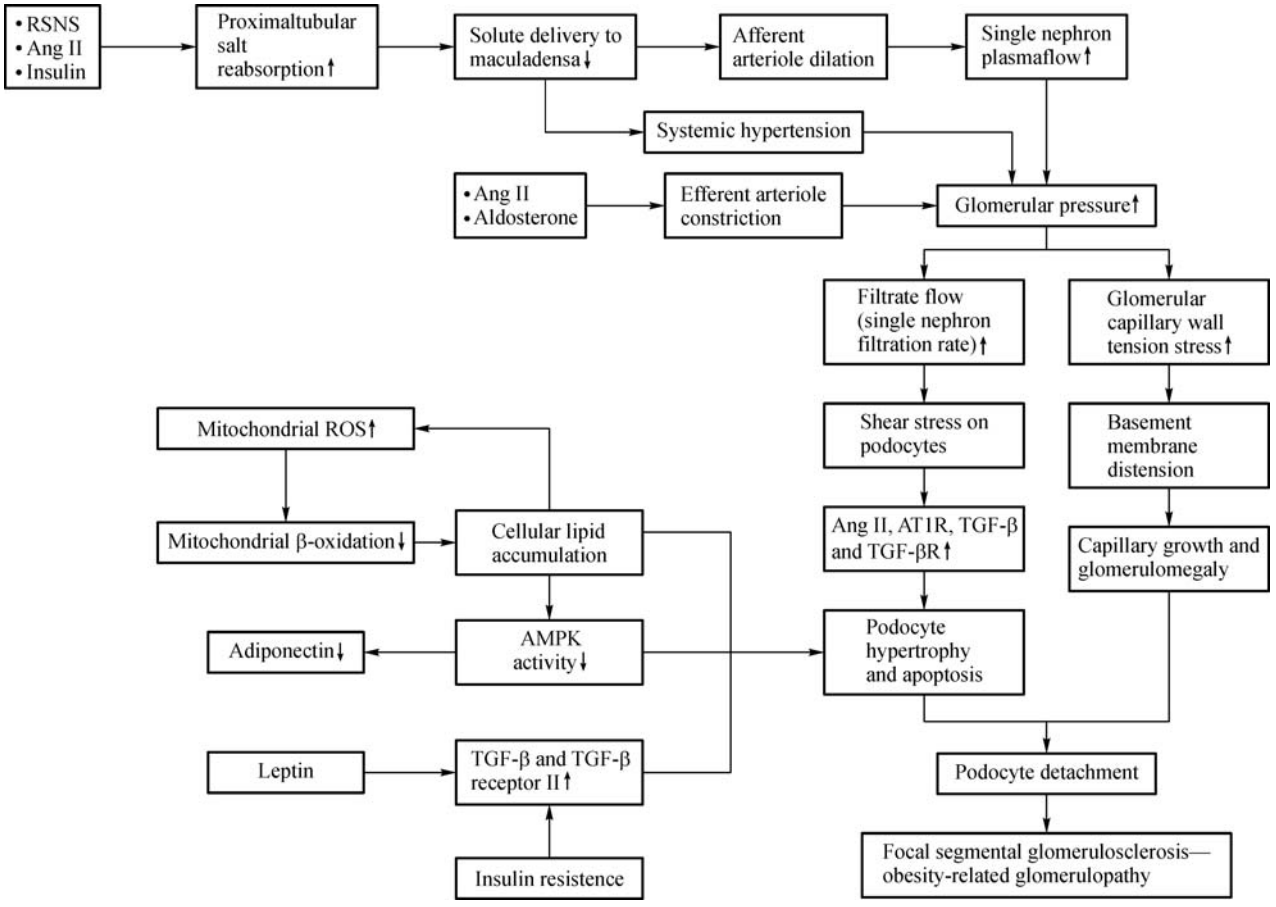

Fig. 2 Ang II, renal sympathetic nervous system, and insulin can cause proximal tubular salt reabsorption that increases glomerular pressure, and efferent arteriole constriction has the same effect. Increase of glomerular pressure leads to the increase of filtrate flow, intensified wall tension, and hypertrophy and apoptosis of podocytes, finally resulting in obesity-related glomerulopathy. Leptin and insulin resistance can promote TGF-β and TGF-β receptor II activities that aggravate podocyte apoptosis. Increase of mitochondrial ROS limits mitochondrial β-oxidation and causes cellular lipid accumulation, which causes a further rise of mitochondrial ROS in return. Lipids can damage mitochondria and decrease AMPK activities, resulting in podocyte apoptosis. Furthermore, adiponectin deficiency can decrease AMPK activity. Ang II, angiotensin II; RSNS, renal sympathetic nervous system; TGF-β, transforming growth factor β; TGF-βR, TGF-β receptor; AT1R, type 1 angiotensin II receptor; AMPK, AMP kinase.

Renal hemodynamic changes

The most important pathogenesis of ORG is glomerular hyperfiltration, hypertension, and hyperperfusion. The hemodynamics of kidneys is indirectly measured by glomerular filtration rate (GFR), renal plasma flow (RPF), and filtration fraction (FF). In 1974, Weisinger *et al.* [19] proposed that the cause of reversible proteinuria in obese patients is renal venous hypertension. Since then, the role of hyperfiltration in glomerular injury has attracted increasing attention. Glomerular hypertension promotes capillary wall stress and leads to basement membrane expansion, glomerulomegaly, and hyperfiltration [20]. Chagnac *et al.* [9] found that the GFR and RPF in the obese group exceeded those of the control by 51% and 31%, respectively. A cross-sectional study of 301 nondiabetic participants also confirmed that obesity is associated with increased GFR, effective renal plasma flow (ERPF), and FF values by comparing lean, overweight, and obese patients with respect to GFR (99, 110, and 117 mL/min, respectively, $P < 0.001$), ERPF (424, 462, and 477 mL/min, respectively, $P < 0.01$), and FF (0.23, 0.24, and 0.25, respectively, $P < 0.001$) [21]. Furthermore, overweight individuals have higher GFR, RPF, and FF values than lean individuals. Meanwhile, several studies showed that renal hemodynamic changes appear at an early stage of adiposity. FF was found to be associated with waist circumference and waist-to-hip ratio apart from BMI. Some studies showed that losing weight, dietary salt restriction, and RAAS blockade can recover increased FF [22]. Chagnac *et al*. [22] demonstrated that ORG hyperfiltration is reversible following weight loss. Notably, improvement in hyperfiltration may prevent the development of overt ORG.

In obese patients, renal vasodilation and RPF increase in the afferent arteriole. Elevation in their GFRs is mainly attributed to increased transcapillary hydraulic pressure difference [9]. Meanwhile, systemic hypertension is extremely common in adiposis, and some studies confirmed its important role in the pathogenesis of renal hyperfiltration.

Hemodynamic changes lead to increases in filtered sodium load accompanied with hyperfiltration in adiposis. Tubular sodium resorption also increases to prevent volume depletion, which may contribute to renal damage and accelerate GFR decline. Reabsorbing glucose and sodium via tubular SGLT2 and SGLT1 results in decreased sodium load to macula densa and distal tubule. This decrease stimulates tubuloglomerular feedback, which induces preglomerular vasodilation and increases GFR, resulting in tubular origin hyperfiltration [23]. Recent studies showed that SLGT2 inhibitors lower the GFR of diabetic patients and have an important protective role in renal hyperfiltration [23,24]. Zingerman *et al.* [25] found that the carboanhydrase inhibitor, acetazolamide, can decrease GFR by 21% in nondiabetic and severely obese patients.

Renin-angiotensin-aldosterone system

Both kidney and adipose tissue contains the major components of RAAS. Adipose tissue products, such as angiotensinogen, increase RAAS activation. Increased levels of angiotensin II and aldosterone more specifically constrict efferent arterioles than afferent arterioles and further raise transcapillary hydraulic pressure difference and GFR. Angiotensin II promotes the production of transforming growth factor-β (TGF-β) and leads to renal fibrosis and podocyte apoptosis [18]. However, some research showed that aldosterone can increase human GFR and promote endothelial dysfunction, inflammation, and fibrosis [26,27]. In obesity cases, RAAS is overactivated and thus may act as an effect factor for renal hyperfiltration.

RAAS overactivation can cause excessive sodium reabsorption, resulting in renal hypertension and hyperfiltration. Angiotensin II stimulates luminal Na^+-H^+ exchanger and basolateral Na^+-K^+-ATPase, thereby increasing sodium reabsorption by the proximal tubule. Angiotensin II also activates epithelial Na^+ channels (ENaCs), thereby enabling the distal tubule to increase its sodium reabsorption. It can also directly activate mineralocorticoid receptors and thus promotes sodium reabsorption and results in positive sodium balance [28].

Insulin resistance

Insulin resistance results in renal hemodynamic changes, especially glomerular hyperfiltration, hypertension, and excessive sodium reabsorption. Hyperinsulinaemia, which is secondary to insulin resistance, increases salt retention. Its mechanism might be excessive sodium reabsorption in the distal tubule through ENaC activation. Insulin resistance causes renal damage, including endothelial dysfunction, increased vascular permeability, protein traffic, mesangial hyperplasia, renal hypertrophy, and enhanced endothelial cell proliferation [29,30]. Some studies showed that insulin activities in podocytes play an essential part in glomerular function and morphology, cytoskeleton remodelling, and survival [29]. Insulin resistance also causes metabolic syndrome, hyperinsulinaemia, adipocytokine dysregulation, and low-grade inflammation [31,32].

Mitochondrial dysfunction

Szeto *et al*. [33] demonstrated mitochondrial dysfunction is the main cause of renal pathology induced by high-fat diet (HFD). Given that the kidney is an organ that demands continuous high-energy provision, mostly from mitochondrial fatty acid β-oxidation (FAO), lipid overload and impaired FAO lead to a disturbance in fatty acid uptake and utilization, further aggravating lipid accumulation in kidney cells and tissue [34]. Renal lipid deposition and downregulated FAO are often present in both obese mice and humans [35]. In previous research, reduction of AMP-activated protein kinase (AMPK) activity was demonstrated to be a downstream consequence of mitochondrial dysfunction [34]. Adiponectin-AMPK pathway downregulates both inflammation and profibrotic pathways in both ORG and diabetic kidney disease [36,37]. AMPK regulates not noly NFκB activation but also NADPH oxidases [36]. AMPK activation can decrease mesangial matrix expansion and lower the levels of profibrotic and proinflammatory markers, such as TGF-β1, tumor necrosis factor-α (TNF-α), and monocyte chemoattracting protein (MCP) -1 [37,38]. Mitochondrial dysfunction generates reactive oxygen species (ROS), which limit mitochondrial β-oxidation and cause cellular lipid accumulation, which results in further increase in mitochondrial ROS levels. Lipids can damage mitochondria and decrease AMPK activity and thus can promote podocyte apoptosis and damage.

Inflammation

Adipose cells release a series of adipokines, such as TNF-α, leptin, adiponectin, interleukins (IL)-6, IL-10, MCP-1, plasminogen activator inhibitor (PAI) -1, resistin, and CRP, and promote chronic low-grade inflammation in obese patients. These lipid-mediated inflammations lead to renal structural and functional changes in obesity cases [39].

Chronic adipose inflammation, which forms from the imbalance between proinflammatory and anti-inflammatory factors, is a major factor for ORG [40].

Obese individuals have high levels of leptin, which binds to specific receptors in mesangial cells. Leptin upregulates TGF-β and TGF-β receptor II, thus inducing an increment of type I and type IV collagen fibers in the mesangium and promoting the formation of fibrosis. Leptin binds to obRb receptors in the hypothalamus and overactivates SNS, which induces renal hemodynamic changes and renal damage [41,42].

Obese individuals have low concentrations of adiponectin. As an anti-inflammatory and insulin-sensitizing factor, adiponectin activates AMPKs to protect podocyte functions and structures by reducing podocyte permeability [43]. Resistin, a proinflammatory factor produced by the monocytemacrophage cells, enhances insulin resistance. The level of resistin reflects the levels of inflammatory factors participating in ORG. Resistin concentration also rises in patients with low GFR. Furthermore, fetuin-A level is elevated in obesity, especially in obesity-related disorders, such as metabolic syndrome, diabetes, and nonalcoholic fatty liver disease. Fetuin-A is associated with increased insulin resistance, inflammation, and fibrosis in the liver and kidney. Fetuin-A also suppresses adiponectin transcription in adipocytes and participates in ORG.

Abnormal lipid metabolism

Abnormal lipid metabolism majorly includes perivascular fat deposits, intracellular lipid load, and fat deposition in the mitochondria. Perivascular fat can regulate blood flow in arteries, and its accumulation is related to exercise-induced albuminuria. Excessive lipid loads cause structural damage and result in capillary loop dysfunction in mesangial cells. Lipid loading produces metabolic abnormalities in insulin and apoptosis in podocytes. Lipids can damage mitochondria and decrease AMPK activity, thereby resulting in podocyte apoptosis. Furthermore, lipid accumulation increases mitochondrial ROS, which causes further amassing of lipids in return.

Others

OSA activates renal SNS and induces sodium retention and hypertension [44]. Renal hemodynamic changes further aggravate ORG. Some studies suggested that a certain extent of protein intake is importantly involved in glomerular hyperfiltration [45].

Innate or acquired glomerular density reduction may be an ORG risk factor. Epidemiological studies showed that CKD risk is significantly high in subjects with low birth weight owing to inadequate intrauterine development. Obese individuals usually have reduced glomerular densities and then are associated with hyperfiltration. Tsuboi demonstrated that patients with biopsy-proven ORG have significantly lower glomerular density than control patients [46].

Clinical manifestation of ORG

The most characteristic and common clinical presentation of ORG is proteinuria with normal urinary sediment, which may or may not be accompanied by renal dysfunction [2,47,48]. In most cases, subnephrotic proteinuria (< 3.5 g/d) is prevalent [48,49]. Some studies reported that about 30% of ORG patients can reach nephrotic range proteinuria but with the characteristic absence of edema, hypoalbuminemia, and typical disproportionate hyperlipidemia of nephrotic syndrome [2,46]. Even in massive proteinuria cases (> 20 g/d), the presence of full nephrotic syndrome is exceptional. The reasons that ORG patients do not develop typical nephrotic syndrome are currently unclear, although may be accounted by the following reasons. First, the slow progression of proteinuria might allow the development of compensation for hepatic metabolism. Second, mechanisms of tubular degradation and reabsorption of filtered proteins in nephropathies caused by ORG may be different from those in other glomerular diseases that cause full nephrotic syndrome [2,8,50–52].

Progressive increase in proteinuria without full nephrotic syndrome can be undetectable for years until late clinical presentation. This characteristic of ORG greatly facilitates the discrimination of ORG from primary FSGS in a full nephrotic syndrome [2,47,51,53]. Table 1 summarizes the main distinctive clinical and histological characteristics of obesity-associated FSGS and primary FSGS.

Several cohort studies showed that obesity is associated with high CKD incidence and increased ESRD risk. The clinical process is indolently evolving, stable, or slowly progressive proteinuria, and 10%–33% of the patients possibly develop progressive renal dysfunction and ESRD. The percentage increases at prolonged follow-ups [2,47,49]. Comparative studies showed that primary FSGS has a more sudden and aggressive disease process than ORG and more easily develops to ESRD [2,47]. Other common clinical manifestations of ORG include hypertension (50%–75% of patients) and dyslipidaemia (70%–80% of patients) [2,47–49].

Treatment strategy of ORG

Various kidney pathology superimposed on ORG is present in patients with obesity. Kidney biopsy assists in

Table 1 Differences between obesity-associated FSGS and primary FSGS

	ORG-related FSGS	Primary FSGS
Appearance of proteinuria	Slowly progressive proteinuria	Proteinuria appears suddenly
Type of the proteinuria	Most with sub-nephrotic proteinuria	Most with nephrotic-range proteinuria
Occurrence of nephrotic syndrome	Absence of nephrotic syndrome (edema, hypoalbuminemia)	Most patients with full nephrotic syndrome
Progression	Slower progression	Faster progression
Variant	Perihilar variant more common	No special type, tip and collapsing variants more common
Glomerular volume	Glomerulomegaly	Normal glomerular volume
Effacement of foot processes in electron microscopy	Irregular effacement of foot processes	Diffuse effacement of foot processes
Serum albumin levels	Normal serum albumin levels	Hypoalbuminaemia is common

performing appropriate management and prognosis [54]. Weight loss and RAAS blockade are the two efficient treatments of ORG. The final aim is to slow down eGFR decline in order to delay ESRD progression.

Weight loss

Weight loss, either by diet or bariatric surgery, reduces the incidence of UAE or proteinuria [2, 47, 55]. That is, weight loss are in a positive correlation with the reduction of incidence of UAE or proteinuria.

Many studies, including nonrandomized prospective studies, randomized controlled trials (RCTs), systematic reviews, and meta-analyses, confirmed the relationship between low-calorie diets and proteinuria reduction [56–58]. Hypertension, metabolic syndrome, diabetes, dyslipidaemia, and salt intake should be controlled at the same time with low-calorie diet.

Weight loss by bariatric surgery is generally much more effective than low-calorie diets [59]. Some clinical reports showed dramatic proteinuria reduction in ORG patients after bariatric surgery. Patients, who underwent bariatric surgeries, including Roux-en-Y gastric bypass, adjustable gastric banding, sleeve gastrectomy, had more severe obesity than dietary intervention patients. In a study, 92 morbidly obese (MO) patients showed that patients with normal renal functions and mild ORG lesions in presurgery period exhibit short- and long-term maintenance of normal renal functions and improvement in both renal arterial hypertension and albuminuria after drastic weight loss after bariatric surgery [60]. Recently, some uncontrolled research indicated that bariatric surgery is beneficial to ORG [61–65]. However, these studies included patients with normal renal functions and minimal albuminuria. For MO patients with CKD, some studies considered that the rate of perisurgical complications is significantly high [66]. Thus, prospective controlled studies in ORG patients with CKD or nephrotic proteinuria are necessary to the evaluation of the efficacy and safety of bariatric surgery [8].

Although some studies showed that weight loss is beneficial to GFR progress [58], these studies often had a short follow-up periods and used a small sample size. The antiproteinuric effect of protection on renal function should be confirmed through large prospective RCTs.

RAAS blockade

The role of RAAS makes it an important target for ORG treatment. RAAS blockade, including angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB), has a significant antiproteinuric effect on ORG patients. Antialdosteronic agents can also decrease proteinuria in obese patients. In retrospective studies, using ACEI or ARB for the treatment obese patients with proteinuria or biopsy-proven ORG obviously decreases proteinuria to 30%–80% of the baseline [2,47,49]. Mallamaci *et al.* [67] confirmed that the antiproteinuric effect of ramipril in obese and overweight patients is more increasingly prominent than those in patients with normal BMI, and that ramipril reduces ESRD incidents. Obese patients are more sensible to antiproteinuric and renoprotective effects of ramipril than nonobese patients.

A prospective RCT compared the effects of weight loss (low-calorie diet or orlistat treatment) with RAAS blockade in obese patients with proteinuria. The antiproteinuric effects of the two groups are similar [68]. Some studies with long follow-up periods suggested that the reduction of proteinuria through RAAS blockers can be exhausted over time, particularly during further weight gain or absence of weight loss [47,49].

Others

Insulin resistance plays an important role in ORG pathogenesis. Some studies reported that insulin-

sensitizing agents, such as thiazolidinedione, alleviate kidney dysfunction and prevent the further worsening of kidney functions. Miyazaki *et al.* [69] showed that type 2 diabetes mellitus patients treated with rosiglitazone for three months had better insulin sensitivity than the placebo group, who had higher serum adiponectin concentration and reduced UAE. An animal experiment showed that metformin improves metabolic disorders, upregulates renal AMPK activity, diminishes the expression of renal TNF-α, decreases renal lipid accumulation, and prevents renal injury [70].

Several animal trials were conducted to discover potential drugs for ORG treatment. Antioxidants, such as SS-31, lycopene, and melatonin, were studied recently. Szeto *et al.* demonstrated that mitochondrial dysfunction is the cause of HFD-induced renal pathology. Herman-Edelstein *et al.* [35] suggested that renal lipid metabolism might be a target for specific therapies aimed at slowing the progression of glomerulosclerosis. Furthermore, SS-31 prevents the loss of glomerular endothelial cells and podocytes, mesangial expansion, glomerulosclerosis, macrophage infiltration, and upregulation of proinflammatory (TNF-α, MCP-1, nuclear factor κ B (NF-κB)) and profibrotic (TGF-β) cytokines. SS-31 is a tetrapeptide that targets cardiolipin, protects mitochondrial cristae structure, and effectively prevents HFD-related renal pathology [33,71]. Meanwhile, targeting the mitochondria may provide a novel strategy for ORG therapy [33]. Pierine *et al.* demonstrated that lycopene might be beneficial in preventing and treating oxidative stress and inflammation in ORG by inhibiting NF-κB and TNF-α [72]. Melatonin has a critical role in the prevention of oxidative mitochondrial damage and exerts beneficial effects on mitochondrial morphology and dynamics [73]. Wang *et al.* [74] confirmed that a low dose of acetaminophen decreases renal lipid deposition, ER-stress related signaling, apoptosis, and albuminuria. These experimental interventions are still in the animal experiment stage and far from human applications. More related research is needed to evaluate the safety and effectiveness of these interventions in human treatment.

Conclusions

We reviewed the clinical and pathological characteristics and pathogenesis of ORG and treatment strategies for this condition. ORG is characterized by glomerulomegaly in the presence or absence of FSGS lesions. Renal hemodynamic changes, renin-angiotensin-aldosterone system, insulin resistance, mitochondrial dysfunction, inflammation, and abnormal lipid metabolism can all contribute to ORG progression. Although subnephrotic proteinuria is the most common ORG manifestation, less than half of ORG patients have nephrotic-range proteinuria. Furthermore, up to one-third of these patients develop progressive renal failure and ESRD, although the clinical course is characterized by stable or slow and progressive proteinuria. Control of obesity and other methods, such as RAAS blockage, can relieve ORG. However, owing to the increase in ORG cases, more studies are necessary to understand the disease.

Compliance with ethics guidelines

Tianhua Xu, Zitong Sheng, and Li Yao declare no conflict of interest. This manuscript is a review article and does not involve a research protocol that requires the approval of the relevant institutional review board or ethics committee.

References

1. Jia W. Obesity in China: its characteristics, diagnostic criteria, and implications. Front Med 2015; 9(2): 129–133
2. Kambham N, Markowitz GS, Valeri AM, Lin J, D'Agati VD. Obesity-related glomerulopathy: an emerging epidemic. Kidney Int 2001; 59(4): 1498–1509
3. D'Agati VD, Chagnac A, de Vries AP, Levi M, Porrini E, Herman-Edelstein M, Praga M. Obesity-related glomerulopathy: clinical and pathologic characteristics and pathogenesis. Nat Rev Nephrol 2016; 12(8): 453–471
4. D'Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. N Engl J Med 2011; 365(25): 2398–2411
5. Serra A, Romero R, Lopez D, Navarro M, Esteve A, Perez N, Alastrue A, Ariza A. Renal injury in the extremely obese patients with normal renal function. Kidney Int 2008; 73(8): 947–955
6. Hughson MD, Hoy WE, Douglas-Denton RN, Zimanyi MA, Bertram JF. Towards a definition of glomerulomegaly: clinical-pathological and methodological considerations. Nephrol Dial Transplant 2011; 26(7): 2202–2208
7. de Vries AP, Ruggenenti P, Ruan XZ, Praga M, Cruzado JM, Bajema IM, D'Agati VD, Lamb HJ, Pongrac Barlovic D, Hojs R, Abbate M, Rodriquez R, Mogensen CE, Porrini E; ERA-EDTA Working Group Diabesity. Fatty kidney: emerging role of ectopic lipid in obesity-related renal disease. Lancet Diabetes Endocrinol 2014; 2(5): 417–426
8. Praga M, Morales E. The fatty kidney: obesity and renal disease. Nephron 2016 Jul 15. [Epub ahead of print] doi:10.1159/000447674
9. Chagnac A, Weinstein T, Korzets A, Ramadan E, Hirsch J, Gafter U. Glomerular hemodynamics in severe obesity. Am J Physiol Renal Physiol 2000; 278(5): F817–F822
10. Fukuda A, Chowdhury MA, Venkatareddy MP, Wang SQ, Nishizono R, Suzuki T, Wickman LT, Wiggins JE, Muchayi T, Fingar D, Shedden KA, Inoki K, Wiggins RC. Growth-dependent podocyte failure causes glomerulosclerosis. J Am Soc Nephrol 2012; 23(8): 1351–1363
11. Liu Y. New insights into epithelial-mesenchymal transition in kidney fibrosis. J Am Soc Nephrol 2010; 21(2): 212–222
12. Matsusaka T, Sandgren E, Shintani A, Kon V, Pastan I, Fogo AB, Ichikawa I. Podocyte injury damages other podocytes. J Am Soc Nephrol 2011; 22(7): 1275–1285

13. Bobulescu IA, Lotan Y, Zhang J, Rosenthal TR, Rogers JT, Adams-Huet B, Sakhaee K, Moe OW. Triglycerides in the human kidney cortex: relationship with body size. PLoS One 2014; 9(8): e101285. doi: 10.1371 /journal.pone.0101285
14. Stefan N, Artunc F, Heyne N, Machann J, Schleicher ED, Häring HU. Obesity and renal disease: not all fat is created equal and not all obesity is harmful to the kidneys. Nephrol Dial Transplant 2016; 31 (5): 726–730
15. Wu Y, Liu Z, Xiang Z, Zeng C, Chen Z, Ma X, Li L. Obesity-related glomerulopathy: insights from gene expression profiles of the glomeruli derived from renal biopsy samples. Endocrinology 2006; 147(1): 44–50
16. Bonnet F, Deprele C, Sassolas A, Moulin P, Alamartine E, Berthezène F, Berthoux F. Excessive body weight as a new independent risk factor for clinical and pathological progression in primary IgA nephritis. Am J Kidney Dis 2001; 37(4): 720–727
17. D'Agati VD, Markowitz GS. Supersized kidneys: lessons from the preclinical obese kidney. Kidney Int 2008; 73(8): 909–910
18. Felizardo RJ, da Silva MB, Aguiar CF, Câmara NO. Obesity in kidney disease: a heavyweight opponent. World J Nephrol 2014; 3 (3): 50–63
19. Weisinger JR, Kempson RL, Eldridge FL, Swenson RS. The nephrotic syndrome: a complication of massive obesity. Ann Intern Med 1974; 81(4): 440–447
20. Kriz W, Lemley KV. A potential role for mechanical forces in the detachment of podocytes and the progression of CKD. J Am Soc Nephrol 2015; 26(2): 258–269
21. Wuerzner G, Pruijm M, Maillard M, Bovet P, Renaud C, Burnier M, Bochud M. Marked association between obesity and glomerular hyperfiltration: a cross-sectional study in an African population. Am J Kidney Dis 2010; 56(2): 303–312
22. Chagnac A, Weinstein T, Herman M, Hirsh J, Gafter U, Ori Y. The effects of weight loss on renal function in patients with severe obesity. J Am Soc Nephrol 2003; 14(6): 1480–1486
23. Novikov A, Vallon V. Sodium glucose cotransporter 2 inhibition in the diabetic kidney: an update. Curr Opin Nephrol Hypertens 2016; 25(1): 50–58
24. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373(22): 2117–2128
25. Zingerman B, Herman-Edelstein M, Erman A, Bar Sheshet Itach S, Ori Y, Rozen-Zvi B, Gafter U, Chagnac A. Effect of acetazolamide on obesity-induced glomerular hyperfiltration: a randomized controlled trial. PLoS One 2015; 10(9): e0137163
26. Nishiyama A, Abe Y. Molecular mechanisms and therapeutic strategies of chronic renal injury: renoprotective effects of aldosterone blockade. J Pharmacol Sci 2006; 100(1): 9–16
27. Ribstein J, Du Cailar G, Fesler P, Mimran A. Relative glomerular hyperfiltration in primary aldosteronism. J Am Soc Nephrol 2005; 16(5): 1320–1325
28. Kawarazaki W, Nagase M, Yoshida S, Takeuchi M, Ishizawa K, Ayuzawa N, Ueda K, Fujita T. Angiotensin II- and salt-induced kidney injury through Rac1-mediated mineralocorticoid receptor activation. J Am Soc Nephrol 2012; 23(6): 997–1007
29. De Cosmo S, Menzaghi C, Prudente S, Trischitta V. Role of insulin resistance in kidney dysfunction: insights into the mechanism and epidemiological evidence. Nephrol Dial Transplant 2013; 28(1): 29–36
30. Chen S, Chen Y, Liu X, Li M, Wu B, Li Y, Liang Y, Shao X, Holthöfer H, Zou H. Association of insulin resistance with chronic kidney disease in non-diabetic subjects with normal weight. PLoS One 2013; 8(9): e74058.doi: 10.1371/journal.pone.0074058
31. Redon J, Lurbe E. The kidney in obesity. Curr Hypertens Rep 2015; 17(6): 555
32. Ye J. Mechanisms of insulin resistance in obesity. Front Med 2013; 7(1): 14–24
33. Szeto HH, Liu S, Soong Y, Alam N, Prusky GT, Seshan SV. Protection of mitochondria prevents high-fat diet-induced glomerulopathy and proximal tubular injury. Kidney Int 2016; 90(5): 997–1011
34. Tang C, Cai J, Dong Z. Mitochondrial dysfunction in obesity-related kidney disease: a novel therapeutic target. Kidney Int 2016; 90(5): 930–933
35. Herman-Edelstein M, Scherzer P, Tobar A, Levi M, Gafter U. Altered renal lipid metabolism and renal lipid accumulation in human diabetic nephropathy. J Lipid Res 2014; 55(3): 561–572
36. Sharma K. Obesity, oxidative stress, and fibrosis in chronic kidney disease. Kidney Int Suppl (2011) 2014; 4(1): 113–117
37. Declèves AE, Zolkipli Z, Satriano J, Wang L, Nakayama T, Rogac M, Le TP, Nortier JL, Farquhar MG, Naviaux RK, Sharma K. Regulation of lipid accumulation by AMP-activated kinase [corrected] in high fat diet-induced kidney injury. Kidney Int 2014; 85(3): 611–623
38. Dugan LL, You YH, Ali SS, Diamond-Stanic M, Miyamoto S, DeCleves AE, Andreyev A, Quach T, Ly S, Shekhtman G, Nguyen W, Chepetan A, Le TP, Wang L, Xu M, Paik KP, Fogo A, Viollet B, Murphy A, Brosius F, Naviaux RK, Sharma K. AMPK dysregulation promotes diabetes-related reduction of superoxide and mitochondrial function. J Clin Invest 2013; 123(11): 4888–4899
39. Manabe I. Chronic inflammation links cardiovascular, metabolic and renal diseases. Circ J 2011; 75(12): 2739–2748
40. Nolan E, O'Meara YM, Godson C. Lipid mediators of inflammation in obesity-related glomerulopathy. Nephrol Dial Transplant 2013; 28(4 Suppl 4): iv22–iv29
41. Young CN, Morgan DA, Butler SD, Mark AL, Davisson RL. The brain subfornical organ mediates leptin-induced increases in renal sympathetic activity but not its metabolic effects. Hypertension 2013; 61(3): 737–744
42. Nasrallah MP, Ziyadeh FN. Overview of the physiology and pathophysiology of leptin with special emphasis on its role in the kidney. Semin Nephrol 2013; 33(1): 54–65
43. Rutkowski JM, Wang ZV, Park AS, Zhang J, Zhang D, Hu MC, Moe OW, Susztak K, Scherer PE. Adiponectin promotes functional recovery after podocyte ablation. J Am Soc Nephrol 2013; 24(2): 268–282
44. Simonds SE, Pryor JT, Ravussin E, Greenway FL, Dileone R, Allen AM, Bassi J, Elmquist JK, Keogh JM, Henning E, Myers MG Jr, Licinio J, Brown RD, Enriori PJ, O'Rahilly S, Sternson SM, Grove KL, Spanswick DC, Farooqi IS, Cowley MA. Leptin mediates the increase in blood pressure associated with obesity. Cell 2014; 159 (6): 1404–1416
45. Ogna A, Forni Ogna V, Bochud M, Guessous I, Paccaud F, Burnier

M, Wuerzner G. Association between obesity and glomerular hyperfiltration: the confounding effect of smoking and sodium and protein intakes. Eur J Nutr 2016; 55(3): 1089–1097

46. Tsuboi N, Utsunomiya Y, Kanzaki G, Koike K, Ikegami M, Kawamura T, Hosoya T. Low glomerular density with glomerulomegaly in obesity-related glomerulopathy. Clin J Am Soc Nephrol 2012; 7(5): 735–741
47. Praga M, Hernández E, Morales E, Campos AP, Valero MA, Martínez MA, León M. Clinical features and long-term outcome of obesity-associated focal segmental glomerulosclerosis. Nephrol Dial Transplant 2001; 16(9): 1790–1798
48. Chen HM, Chen Y, Zhang YD, Zhang PP, Chen HP, Wang QW, Li LS, Liu ZH. Evaluation of metabolic risk marker in obesity-related glomerulopathy. J Ren Nutr 2011; 21(4): 309–315
49. Tsuboi N, Koike K, Hirano K, Utsunomiya Y, Kawamura T, Hosoya T. Clinical features and long-term renal outcomes of Japanese patients with obesity-related glomerulopathy. Clin Exp Nephrol 2013; 17(3): 379–385
50. Praga M, Borstein B, Andres A, Arenas J, Oliet A, Montoyo C, Ruilope LM, Rodicio JL. Nephrotic proteinuria without hypoalbuminemia: clinical characteristics and response to angiotensin-converting enzyme inhibition. Am J Kidney Dis 1991; 17(3): 330–338
51. Praga M, Morales E, Herrero JC, Pérez Campos A, Domínguez-Gil B, Alegre R, Vara J, Martínez MA. Absence of hypoalbuminemia despite massive proteinuria in focal segmental glomerulosclerosis secondary to hyperfiltration. Am J Kidney Dis 1999; 33(1): 52–58
52. Sethi S, Zand L, Nasr SH, Glassock RJ, Fervenza FC. Focal and segmental glomerulosclerosis: clinical and kidney biopsy correlations. Clin Kidney J 2014; 7(6): 531–537
53. Sethi S, Glassock RJ, Fervenza FC. Focal segmental glomerulosclerosis: towards a better understanding for the practicing nephrologist. Nephrol Dial Transplant 2015; 30(3): 375–384
54. Salvatore SP, Chevalier JM, Kuo SF, Audia PF, Seshan SV. Kidney disease in patients with obesity: It is not always obesity-related glomerulopathy alone. Obes Res Clin Pract2017 Apr 22. [Epub ahead of print] doi: 10.1016/j.orcp.2017.04.003
55. Saiki A, Nagayama D, Ohhira M, Endoh K, Ohtsuka M, Koide N, Oyama T, Miyashita Y, Shirai K. Effect of weight loss using formula diet on renal function in obese patients with diabetic nephropathy. Int J Obes 2005; 29(9): 1115–1120
56. Bolignano D, Zoccali C. Effects of weight loss on renal function in obese CKD patients: a systematic review. Nephrol Dial Transplant 2013; 28(Suppl 4): iv82–iv98
57. Friedman AN, Chambers M, Kamendulis LM, Temmerman J. Short-term changes after a weight reduction intervention in advanced diabetic nephropathy. Clin J Am Soc Nephrol 2013; 8(11): 1892–1898
58. Morales E, Valero MA, León M, Hernández E, Praga M. Beneficial effects of weight loss in overweight patients with chronic proteinuric nephropathies. Am J Kidney Dis 2003; 41(2): 319–327
59. 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): 1173–1183
60. Serra A, Esteve A, Navarro-Díaz M, López D, Bancu I, Romero R. Long-term normal renal function after drastic weight reduction in patients with obesity-related glomerulopathy. Obes Facts 2015; 8 (3): 188–199
61. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Brethauer SA, Navaneethan SD, Aminian A, Pothier CE, Kim ES, Nissen SE, Kashyap SR; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes—3-year outcomes. N Engl J Med 2014; 370(21): 2002–2013
62. MacLaughlin HL, Hall WL, Patel AG, Macdougall IC. Laparoscopic sleeve gastrectomy is a novel and effective treatment for obesity in patients with chronic kidney disease. Obes Surg 2012; 22 (1): 119–123
63. Neff KJ, Frankel AH, Tam FW, Sadlier DM, Godson C, le Roux CW. The effect of bariatric surgery on renal function and disease: a focus on outcomes and inflammation. Nephrol Dial Transplant 2013; 28(Suppl 4): iv73–iv82
64. Reid TJ, Saeed S, McCoy S, Osewa AA, Persaud A, Ahmed L. The effect of bariatric surgery on renal function. Surg Obes Relat Dis 2014; 10(5): 808–813
65. Saleh F, Kim SJ, Okrainec A, Jackson TD. Bariatric surgery in patients with reduced kidney function: an analysis of short-term outcomes. Surg Obes Relat Dis 2015; 11(4): 828–835
66. Lieske JC, Mehta RA, Milliner DS, Rule AD, Bergstralh EJ, Sarr MG. Kidney stones are common after bariatric surgery. Kidney Int 2015; 87(4): 839–845
67. Mallamaci F, Ruggenenti P, Perna A, Leonardis D, Tripepi R, Tripepi G, Remuzzi G, Zoccali C; REIN Study Group. ACE inhibition is renoprotective among obese patients with proteinuria. J Am Soc Nephrol 2011; 22(6): 1122–1128
68. Patil MR, Mishra A, Jain N, Gutch M, Tewari R. Weight loss for reduction of proteinuria in diabetic nephropathy: comparison with angiotensin-converting enzyme inhibitor therapy. Indian J Nephrol 2013; 23(2): 108–113
69. Miyazaki Y, Cersosimo E, Triplitt C, DeFronzo RA. Rosiglitazone decreases albuminuria in type 2 diabetic patients. Kidney Int 2007; 72(11): 1367–1373
70. Zhang SQ, Sun YT, Xu TH, Zhang XF, Liu YZ, Ma MJ, Wang LN, Yao L. Protective effect of metformin on renal injury of C57BL/6J mouse treated with high fat diet. Pharmazie 2014; 69(12): 904–908
71. Birk AV, Chao WM, Bracken C, Warren JD, Szeto HH. Targeting mitochondrial cardiolipin and the cytochrome c/cardiolipin complex to promote electron transport and optimize mitochondrial ATP synthesis. Br J Pharmacol 2014; 171(8): 2017–2028
72. Pierine DT, Navarro ME, Minatel IO, Luvizotto RA, Nascimento AF, Ferreira AL, Yeum KJ, Corrêa CR. Lycopene supplementation reduces TNF-α via RAGE in the kidney of obese rats. Nutr Diabetes 2014; 4(11): e142
73. Stacchiotti A, Favero G, Giugno L, Lavazza A, Reiter RJ, Rodella LF, Rezzani R. Mitochondrial and metabolic dysfunction in renal convoluted tubules of obese mice: protective role of melatonin. PLoS One 2014; 9(10): e111141. DOI:10.1371/journal. pone. 0111141
74. Wang C, Wu M, Arvapalli R, Dai X, Mahmood M, Driscoll H, Rice KM, Blough E. Acetaminophen attenuates obesity-related renal injury through ER-mediated stress mechanisms. Cell Physiol Biochem 2014; 33(4): 1139–1148