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REVIEW

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Obesity-related glomerulopathy: Current approaches and future perspectives

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Summary

Obesity-related glomerulopathy (ORG) is a silent comorbidity which is increasing in incidence as the obesity epidemic escalates. ORG is associated with serious health consequences including chronic kidney disease, end-stage renal disease (ESRD), and increased mortality. Although the pathogenic mechanisms involved in the development of ORG are not fully understood, glomerular hemodynamic changes, renin-angiotensin-aldosterone system (RAAS) overactivation, insulin-resistance, inflammation and ectopic lipid accumulation seem to play a major role. Despite albuminuria being commonly used for the non-invasive evaluation of ORG, promising biomarkers of early kidney injury that are emerging, as well as new approaches with proteomics and metabolomics, might permit an earlier diagnosis of this disease. In addition, the assessment of ectopic kidney fat by renal imaging could be a useful tool to detect and evaluate the progression of ORG. Weight loss interventions appear to be effective in ORG, although large-scale trials are needed. RAAS blockade has a renoprotective effect in patients with ORG, but even so, a significant proportion of patients with ORG will eventually progress to ESRD despite therapeutic efforts. It is noteworthy that certain antidiabetic agents such as sodium-glucose cotransporter 2 inhibitors (SGLT2i) or glucagon-like peptide-1 receptor agonists (GLP-1 RAs) could be useful in the treatment of ORG through different pleiotropic effects. In this article, we review current approaches and future perspectives in the care and treatment of ORG.

KEYWORDS
albuminuria, kidney, nephroprotection, obesity

1 | INTRODUCTION

Overweight, defined as a body mass index (BMI) 25 to <30 kg/m^2, and obesity, defined as a BMI ≥ 30 kg/m^2, result from an imbalance between calorie intake and energy expenditure, in which unhealthy dietary habits and a sedentary lifestyle play an important role.[1] Excess body weight is associated with several comorbidities, including type 2 diabetes mellitus (T2DM), cardiovascular disease, dyslipidemia, hypertension, obstructive sleep apnea, hypogonadism, infertility, non-alcoholic fatty liver disease, osteoarthritis, esophageal reflux disease, and some types of cancer.[2]

Renal involvement due to obesity, called obesity-related glomerulopathy (ORG), is an increasing condition, parallel to the current obesity epidemic. Accordingly, extensive studies of longitudinal cohorts in individuals without known kidney disease have shown that the increase in BMI is associated with the development of proteinuria, a lower estimated glomerular filtration rate (eGFR), and a higher incidence of end-stage renal disease (ESRD).[3,4] Moreover, an increased risk of severe renal outcomes (ESRD or chronic kidney disease [CKD]-related death) has been reported with a BMI ≥ 25 kg/m^2, with the steepest increase in hazard ratio (HR) in participants with a BMI of 30 kg/m^2 or greater.[5]

Interestingly, with a worldwide prevalence of CKD varying between 10.5% and 13%,[6] several population-based studies have reported that ORG could play a key pathogenic role in approximately 15%–30% of patients with CKD.[7,8] In this regard, obesity, which is closely related to CKD progression regardless of its etiology, can aggravate a number of primary kidney diseases, thus worsening the prognosis and health outcomes.[9,10]

It is also important to highlight that the central abdominal fat distribution characteristic of the metabolic syndrome (MetS) constitutes an independent risk factor for renal impairment, even after adjusting for traditional CKD risk predictors, such as T2DM and hypertension.[11,12] Therefore, in the REGARDS study, different models stratified by weight and metabolic health showed that incident ESRD among participants was higher in subjects with MetS who had obesity/overweight, in comparison with normal-weight subjects without MetS.[13] Also, several analyses from the National Health and Nutrition Examination Survey (NHANES) revealed that abdominal obesity is independently associated with albuminuria, even in the presence of normal blood pressure levels and glucose concentrations.[14]

On the other hand, the current epidemic of childhood obesity may also translate into an increased risk of CKD and ESRD in later life, as the development of obesity at this stage may trigger early renal functional and morphological alterations, although the exact mechanisms involved in this association are not fully understood.[15,16] At this point, it is important to take into account that some early life determinants could have a role in this connection. In line with this, low birth weight has been linked to reduced nephron mass and increased weight gain during childhood and adolescence, which may predispose to more rapid renal impairment.[17] In addition, an adverse intrauterine environment also results in a low nephron number and may contribute to fetal metabolic programming and childhood obesity, which would act as an additive factor in renal impairment.[18,19]

Unfortunately, ORG may go unnoticed for years, due to the absence of clinical manifestations, and remain undetected until stages in which renal function is already severely impaired and the prognosis is severely compromised. Considering all these factors together, developing strategies to identify patients at high risk for developing ORG and designing effective therapeutic approaches for this condition should be considered a health priority.

In this review, we summarize the current knowledge on the pathophysiology, diagnosis, and therapeutic management of ORG and highlight future perspectives in the evaluation, care, and treatment of this condition.

2 | ORG PATHOPHYSIOLOGY

Despite the fact that all the pathophysiological mechanisms through which obesity can induce kidney disease are not fully clarified, the most well-recognized mechanisms include glomerular hyperfiltration, overactivation of the renin-angiotensin-aldosterone system (RAAS), hyperinsulinemia and insulin resistance, increased release of pro-inflammatory cytokines, and ectopic lipid accumulation and lipotoxicity (Figure 1).

2.1 | Hemodynamic changes and hyperfiltration

Glomerular hyperfiltration represents the central mechanism of renal injury in ORG.[20] In this regard, obesity is associated with vasodilatation of the afferent arteriole, resulting in increased renal plasma flow, eGFR, and filtration fraction.[20] In addition, increased intra-glomerular pressure drives glomerular filtration barrier injury, causing glomerulomegaly, podocyte hypertrophy, and apoptosis.[8,21]

In addition, according to the tubulocentric hypothesis, obesity-related hyperfiltration could also have a tubular origin.[8] Therefore, obesity facilitates sodium reabsorption in the proximal tubule, resulting in decreased solute delivery to the macula densa and deactivation of tubuloglomerular feedback (TGF).[8,21] Sodium reabsorption via increased distal tubular epithelial Na^+ channel (ENac) activation is also a consequence of angiotensin II overproduction, becoming TGF less responsive.[22] Overall, these mechanisms can lead to decreased preglomerular vascular resistance and subsequently to vasodilation of the glomerular afferent arteriole, increasing the eGFR.[8,22]

Finally, it is also important to highlight the impact of hypertension or T2DM (both highly prevalent in obesity) on renal outcomes in ORG.[23] These two conditions contribute to hyperfiltration and glomerular hypertension due to increased renal plasma flow and

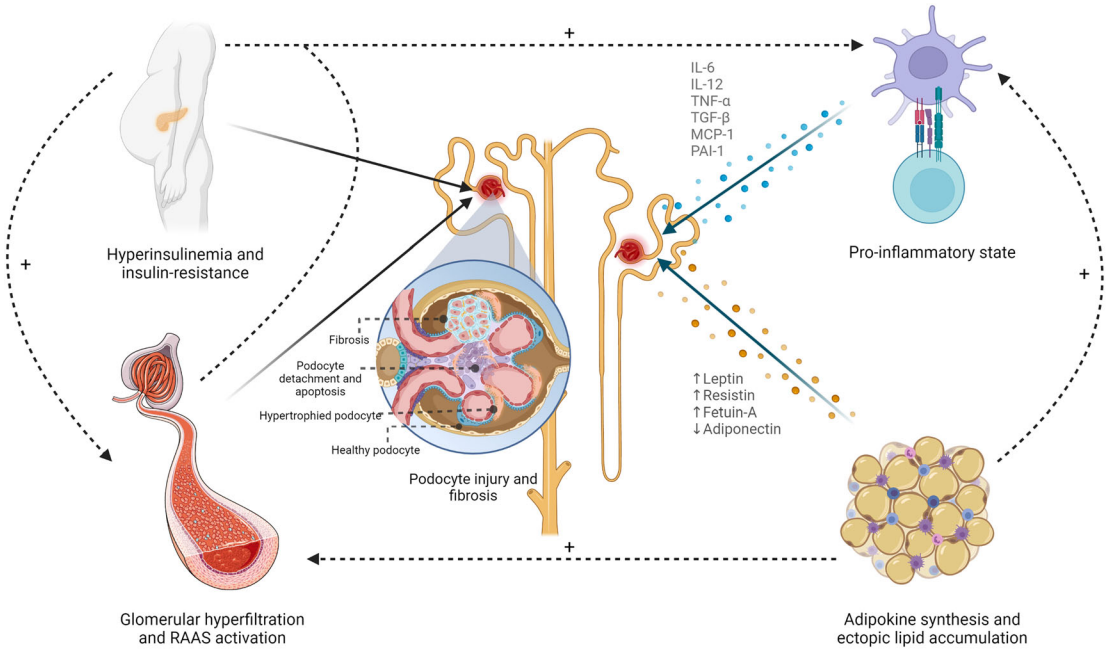

FIGURE 1 Pathogenic mechanisms involved in obesity-related glomerulopathy (ORG). In obesity, glomerular hyperfiltration and RAAS overactivation lead to podocyte injury and fibrogenesis. Inflammatory agents promote different glomerular changes, favoring fibrosis and proteinuria. Ectopic lipid accumulation prompts glomerular damage through lipotoxicity and mechanical compression; synthesized adipokines also have pro-inflammatory and vasoconstrictive properties. Hyperinsulinemia and insulin resistance can induce podocyte dysfunction and glomerulosclerosis directly and via stimulation of hemodynamic changes and pro-inflammatory cytokine production. RAAS, renin-angiotensin-aldosterone system; IL, interleukin; TNF-α, tumor necrosis factor α; TGF-β, transforming growth factor β; MCP -1, monocyte chemoattractant protein-1; PAI-1, plasminogen activator inhibitor-1

impaired autoregulatory capacity and may amplify kidney damage in patients with ORG.[23]

2.2 | Activation of the RAAS

RAAS overactivation in obesity is closely related to hemodynamic changes and hyperfiltration, and plays a major role in the pathogenesis and perpetuation of ORG. It is thought to be secondary to different factors: (a) mechanical hemodynamic changes that result in the compression of the renal hilum and parenchyma by visceral fat; (b) raised intra-abdominal pressure; and (c) direct hormonal synthesis of different components of the RAAS by visceral fat and neurohormonal stimulation induced by the sympathetic system (also related to hyperleptinemia and insulin resistance).[24]

Angiotensin II and aldosterone regulate vasomotor tone with a predominant vasoconstrictive effect, especially on the efferent arteriole, increasing hydrostatic glomerular pressure and eGFR. Notably, increased angiotensin II secretion from abdominal adipose tissue has been demonstrated in obesity.[25] Moreover, some studies have shown that plasma aldosterone levels are disproportionately elevated in patients with hypertension and obesity, particularly in those with abdominal obesity.[26] It should be pointed out that aldosterone stimulates the activation of ENac and also suppresses TGF, leading to hyperfiltration, factors that contribute to renal injury in ORG.[27] These data suggest that subjects with obesity could be particularly sensitive to the recently emphasized antiproteinuric, renoprotective, and cardioprotective effects of spironolactone and other aldosterone antagonists.[28]

2.3 | Synergy between obesity and low nephron number

It has been suggested that obesity could be a key factor determining the poor evolution of renal function.[29] Although the appearance of renal abnormalities (slowly progressive proteinuria and renal insufficiency) is relatively uncommon after unilateral nephrectomy, a clinical study showed that BMI at the time of nephrectomy and during follow-up was significantly higher among patients who developed these abnormalities in comparison with patients who did not.[30] Also, González et al., in a study of 54 patients with unilateral renal agenesis or remnant kidneys, found that BMI was the only clinical variable statistically associated with the risk of developing proteinuria and renal failure progression.[31]

Interestingly, reduced nephron mass may also have a congenital origin, owing to inadequate intrauterine development. Epidemiological studies have shown that the risk of ESRD is significantly higher in subjects with birth weight below the 10th percentile,[32] and the occurrence of obesity in later life could have important consequences in the progression of kidney disease.[17]

2.4 | Hyperinsulinemia

Insulin resistance and compensatory hyperinsulinemia have a major impact on hemodynamic changes and also promote chronic inflammation in ORG. Elevated insulin levels are associated with preglomerular vasodilatation and glomerular hypertension.[33] Insulin resistance has been associated with the onset of albuminuria, as well as with the decline in renal function in individuals with obesity without diabetes.[34,35] Insulin is also essential in podocyte function, morphology, and survival, leading insulin resistance to podocyte apoptosis and hypertrophy of the remaining podocytes, resulting in glomerulosclerosis.[36]

2.5 | Adipokines, inflammatory agents, and oxidative stress

Visceral adipose tissue is an active endocrine organ that constitutes an important source of cytokine secretion with systemic effects, including kidney signaling molecules and hormones with a significant role in the pathogenesis of ORG.[8,11] Therefore, excess body weight is associated with increased circulating levels of several pro-inflammatory adipokines, such as leptin, resistin or fetuin-A, and reactive oxygen species (ROS).[8,11]

Leptin has been associated with increased sympathetic vascular tone and renal sodium reabsorption, leading to hyperfiltration, and transforming growth factor β (TGF-β) overexpression, correlating with renal fibrosis and proteinuria.[37] In contrast, adiponectin, which is decreased in subjects with obesity, is an anti-inflammatory, anti-atherogenic, and insulin-sensitizing adipokine.[38] Adiponectin exerts a protective role on podocytes, stimulating the AMP-activated protein kinase (AMPK) which downregulates inflammatory and profibrotic pathways in ORG.[39–41] Resistin upregulates various inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), and interleukin 12 (IL-12).[42] Fetuin-A is associated with insulin resistance, ectopic lipid accumulation, and increased levels of pro-inflammatory cytokines.[43] Different inflammatory agents, such as plasminogen activator inhibitor-1 (PAI-1), nuclear factor-kappa B (NF-κB), and monocyte chemoattractant protein-1 (MCP-1) may also play a relevant role in the pathogenesis of ORG.[44,45]

2.6 | Altered lipid metabolism, ectopic lipid accumulation, and lipotoxicity

In 1982, Moorhead's lipid nephrotoxicity hypothesis was postulated to explain how hyperlipidemia and renal lipid accumulation may aggravate kidney injury and dysfunction.[46] In this regard, increased fat accumulation in perirenal and pararenal spaces in subjects with obesity might impair renal function.[47–49] Moreover, free fatty acids (FFAs) and adipokines released from perirenal fat reach the kidney cortex, exacerbating intrarenal damage through lipotoxicity by increasing FFAs metabolites.[49,50] Ectopic accumulation of fat in perirenal and pararenal spaces also physically compresses renal vessels and parenchyma, increasing renal interstitial hydrostatic pressure and reducing tubular blood flow.[51]

In addition, de novo renal lipogenesis may be a key driver of renal lipotoxicity in ORG.[52] Accordingly, it has been reported that in animal models and in patients with overweight/obesity and CKD, adenosine triphosphate (ATP)-citrate lyase (ACL) is overstimulated in podocytes, mesangial cells, and tubular cells, leading to an excess of acetyl-CoA, the substrate for de novo lipogenesis and histone acetylation, which promotes renal injury by ectopic lipid accumulation and fibrogenesis.[52] In addition, sterol regulatory element-binding proteins (SREBPs) may also mediate renal lipotoxicity through de novo lipogenesis, although they can also produce renal injury via lipid-independent pathways.[53,54]

2.7 | The role of genetics in ORG

Some studies have investigated gene expression in the glomeruli of patients with ORG, reporting an upregulation of the glomerular gene expression profiles related to inflammatory cytokines, lipid metabolism, and insulin resistance.[55] Similarly, genetic polymorphisms associated with adiposity have been demonstrated to be closely related to CKD.[56]

Despite these advances, further research in this field is still needed, including the development of novel renal biopsy analysis techniques and functional genomics, which in the following years could potentially allow for targeted therapeutic approaches for ORG.

3 | HISTOPATHOLOGICAL FINDINGS IN ORG

Intrarenal hemodynamic disorders favor the development of the characteristic lesions of ORG: oligonephronia (low glomerular density) and glomerulomegaly (glomerular hypertrophy). Glomerulomegaly (Figure 2) is the pathological hallmark of the disease and consists of glomerular hypertrophy as a consequence of functional adaptations observed in ORG, ultimately represented by glomerular hyperfiltration.[8,57] Low glomerular density may be closely related to the pathogenesis of renal injury in ORG, leading to the adaptive glomerulomegaly, which secondarily aggravates the loss of nephron mass due to the harmful consequences of increased intraglomerular pressure.[58]

Glomerulomegaly may be also accompanied by focal segmental glomerulosclerosis (FSGS), although a lower percentage of glomeruli are usually affected by these lesions in comparison with primary FSGS, which suggests that ORG is a milder and slower progressive form of FSGS.[8,57] Despite the fact that segmental sclerosis can compromise any part of the glomeruli, the perihilar involvement, which is mainly observed in the hypertrophic glomeruli, is commonly found in ORG (Figure 2), and may be explained by the higher elevation of filtration pressure at the afferent capillary network.[8,57] Interstitial fibrosis

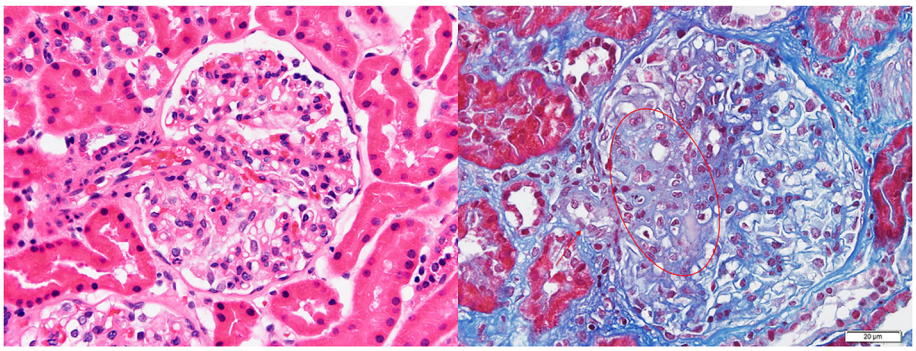

FIGURE 2 Histopathology of ORG. Two glomeruli at the same magnification (40×). The one on the left (HE) corresponds to a normal glomerulus of a patient without glomerular disease. The one on the right (Masson) corresponds to a patient with obesity with glomerulomegaly; a clear difference in size can be seen. Also, the glomerulus on the right shows a perihilar segmental sclerosing lesion (red circle; the hilum red arrow). Glomerulomegaly is defined as a glomerulus that is more than 1.5 times the size of a normal glomerulus (approx. 250 microns) or as a glomerulus that occupies more than half of a 40× field

and tubular atrophy, along with arteriosclerotic lesions, may also be present before evidence of clinical renal involvement.[59] Other typical features in ORG are the slight and irregular erasure of podocytes, as opposed to the relatively diffuse effacement characteristic of primary FSGS, and the presence of non-specific deposits of IgM and C3 in lesions of sclerosis and hyalinosis on immunofluorescence, with the absence of deposition of immune complexes.[57]

Some patients with ORG can also present focal diabetoid changes (increase in mesangial matrix and mild focal mesangial sclerosis, mild focal thickening of glomerular, and tubular basement membranes)[57] even without clinical evidence of impaired glucose metabolism, in consonance with the similar pathophysiological mechanisms that ORG and diabetic nephropathy share.[60] In addition, intracellular lipid vacuoles can be found in some specific cell types, such as proximal tubular epithelial cells, podocytes, and mesangial cells, as a result of excessive lipid accumulation.[49,61]

It is important to bear in mind that there may be a broad spectrum of kidney pathology beyond ORG in patients with obesity and renal disease. In line with this, in a recent study including 248 renal biopsies from patients with morbid obesity and kidney disease (nephrotic range proteinuria mostly), lesions compatible with ORG were only detected in 73 patients (29 patients with ORG alone and 44 patients with ORG and another kidney disease), whereas 167 patients presented other kidney diseases alone (diabetic nephropathy, acute tubular necrosis, or hypertensive nephrosclerosis, among others), without ORG.[62] These findings highlight that kidney biopsy is a useful technique to guide management and prognosis in patients with severe obesity and kidney disease.[62]

4 | ORG EVALUATION AND DIAGNOSIS

4.1 | Clinical presentation

The most common clinical presentation of ORG is the detection of proteinuria, along with normal urinary sediment, in a patient with obesity, in the absence of other causes of kidney injury.[8,63–65] Without therapeutic interventions, the usual clinical course of ORG is characterized by stable or slowly progressive proteinuria; however, up to one third of patients with ORG may develop proteinuria in the nephrotic range (defined by an excretion >3.5 g of proteinuria/day), and a small percentage of patients may even show massive proteinuria (>20 g of proteinuria/day), although this presentation is very unusual.[8,64–66] Despite the possible presence of massive proteinuria values, patients with ORG secondary to hyperfiltration do not normally develop hypoalbuminemia or other characteristics of nephrotic syndrome.[63,64,66] Moreover, long-term outcomes in different cohorts assessing the clinical course of ORG have revealed that this entity involves an increased risk of progression to renal failure and ESRD.[63,64]

Furthermore, a significant percentage of patients may develop hypertension and dyslipidemia (although these comorbidities may also be present before the onset of ORG, due to obesity itself).[8,63,64]

Although more studies are needed, baseline age, serum creatinine, proteinuria, and time-averaged proteinuria during follow-up have been described as risk factors associated with ORG progression.[64]

4.2 | Evaluation of kidney function in obesity

The correct estimation of renal function in patients with obesity is essential not only for staging CKD and monitoring disease progression but also for drug dosing adjustments. Indeed, a large number of formulas to estimate GFR have been developed in recent decades, mostly based on creatinine or cystatin C, some of which are widely accepted for clinical use in obesity. Among these, it has been reported that the CKD-EPI equation offers a good GFR prediction for eGFR < 60 ml/min/1.73 m^2 in individuals with a BMI < 40 kg/m^2.[67]

However, estimating GFR by formulas usually fails in reflecting real renal function in patients with overweight and obesity.[68] In line with this, in a study including more than 900 participants with overweight/obesity with or without CKD, in which 56 creatinine/cystatin

C-based equations were evaluated, López-Martínez et al. reported that the error of eGFR by any equation was wide and frequent, compared with measured GFR (plasma clearance of iohexol), and it was even larger in formulas including weight or height.[68] Also, the adjustment of eGFR/measured GFR by body surface area (BSA) results in a relevant error and implies a significant underestimation of renal function in subjects with overweight and obesity.[68] Moreover, it should be noted that the measurement of creatinine clearance to estimate GFR can also lead to error, as tubular secretion of creatinine accounts for around 10%–20% of urinary creatinine in subjects with normal GFR, and this percentage progressively increases as GFR declines, resulting in significant overestimation of GFR, especially among patients with advanced CKD.[69] In addition, creatinine clearance can be imprecise in patients with overweight/obesity, as previously demonstrated.[68] Therefore, some authors have recommended using a gold standard method (e.g., inulin or iohexol plasma clearance) in subjects with obesity, although these techniques are not widely used given the limited availability and the impracticality in daily clinical routine.[68] Alternatively, transdermal glomerular filtration rate measurement using clearance of fluorescent tracers may become a practical approach in this population, although further research is warranted.[70]

TABLE 1 Potential early biomarkers of kidney injury in ORG

Biomarker	Localization	Reference
KIM-1	Proximal tubule	74
Cys C	Glomerulus, proximal tubule	75
NAG	Proximal tubule, distal tubule	74
NGAL	Proximal tubule, distal tubule	75
Podocin	Glomerulus	78,79
Nephrin	Glomerulus	78,79
Podocin:nephrin ratio	Glomerulus	79
PCX	Glomerulus	78,80
GluAp, AlaAp	Glomerulus, proximal and distal tubule	81
Klotho	Proximal and distal tubule, collecting duct	81
OPN	Proximal tubule, distal tubule	75,82
Netrin-1	Proximal tubule	83

Abbreviations: AlaAp, alanyl aminopeptidase; Cys C, cystatin C; GluAp, glutamyl aminopeptidase; KIM-1, kidney injury molecule 1; NAG, *N*-acetyl-beta-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; OPN, osteopontin; PCX, podocalyxin.

4.3 | Markers of kidney damage

Although the determination of albuminuria/proteinuria is widely used for the non-invasive assessment of kidney disease, it is not always an early marker of kidney injury. Indeed, structural renal changes may be present before renal dysfunction or the detection of classic markers of kidney damage. Therefore, in a previous study conducted in subjects with morbid obesity undergoing bariatric surgery, histological changes consistent with ORG were detected in some patients despite normal renal function and absence of albuminuria.[59]

Hence, in recent years, new biomarkers have been pursued for the diagnosis of kidney tubular injury in the early stages, although the majority of them need to be properly assessed in well-designed intervention studies, as studies conducted in humans are limited and they rest on post-hoc analysis. Among these new biomarkers, the most promising are urinary kidney injury molecule-1 (KIM-1), urinary cystatin C, urinary *N*-acetyl-beta-D-glucosaminidase (NAG) and urinary neutrophil gelatinase-associated lipocalin (NGAL), a classic biomarker of renal injury also described in ORG (Table 1).[71,72] The overexpression of these molecules in subjects with obesity has been reported mainly in the pediatric population.[73–75] Interestingly, some of these tubular markers are also related to renal injury in the early stages of T2DM and could be useful to predict CKD progression.[72,76] In this regard, urinary cystatin C has been identified as a predictor of the progression of T2DM nephropathy,[72] whereas urinary NGAL and KIM-1 have been associated with a faster decline in eGFR in patients with T2DM.[76] Besides this, ectopic lipid accumulation, which is discussed in previous sections, must be also considered as a promising novel biomarker of renal injury in patients with ORG.[49]

Several studies have revealed an additional number of new biomarkers of early glomerular injury in ORG. Urinary podocin and nephrin (as well as urinary podocin/nephrin ratio) are specific markers of glomerular podocyte injury/stress and are associated with the progression of CKD.[77–79] Urinary podocalyxin (PCX), a podocyte surface antigen, was elevated in subjects with obesity and a normal eGFR and urinary albumin/creatinine ratio (ACR) compared with individuals without obesity.[80] Urinary glutamyl aminopeptidase (GluAp), alanyl aminopeptidase (AlaAp), and Klotho have also been associated with early diagnosis and prognosis of renal lesions in Zucker obese rats and, together with urinary osteopontin and netrin-1, can be considered potential markers of renal injury and fibrosis (Table 1).[81–83] However, it is important to highlight that these biomarkers still remain hypothetical, and further research is needed to confirm their usefulness in the early assessment of ORG with large population studies.

Another useful tool to predict kidney damage could be the urinary proteome, as proteomic changes may precede the development of overt disease.[71] In this regard, the CKD273 classifier, a panel formed by 273 urinary peptides, has been validated in cross-sectional and longitudinal studies, allowing early detection of CKD as well as predicting the course of the disease.[84] Accordingly, a high-risk score with the CKD273 classifier has been associated with progression to microalbuminuria over a median of 2.5 years in a large cohort study including patients with T2DM and normoalbuminuria.[85]

Moreover, a new specific classifier to detect ORG called BMI150 has recently been developed. Based on 150 urinary peptides (most of them collagen fragments), BMI150 has been reported to identify accurately patients without diabetes with a BMI > 30 kg/m^2 and an eGFR <45 ml/min/1.73 m^2, distinguishing between subjects without diabetes with and without obesity and nephropathy with either preserved

or reduced renal function (except in advanced stages of CKD) in an independent cohort.[86]

4.4 | Renal imaging

The ectopic accumulation of lipids in the kidney (fatty kidney) may constitute an excellent biomarker of ORG, and renal imaging has therefore become a very useful tool to detect and evaluate the progression of ORG.[49,87] Currently, the most widely used imaging techniques to evaluate the fatty kidney are renal ultrasonography and ultrasound elastography, computed tomography (CT), and magnetic resonance imaging (MRI) (Table 2).

4.4.1 | Ultrasonography and ultrasound elastography

As a result of their relatively easy access and low cost, ultrasonography and ultrasound elastography could offer the possibility of evaluating structural changes over time in ORG and detecting renal fibrosis.[88] In this regard, color Doppler ultrasonography enables the assessment of intrarenal blood flow and hemodynamic changes, using various parameters that can evaluate early vascular alterations. A pathologic resistance index (RI) of the intrarenal vessels, particularly the interlobar arteries, is considered the most useful indicator of renal perfusion changes and early signs of renal damage.[89–91] In addition, contrast-enhanced ultrasonography may permit the evaluation of

TABLE 2 Studies assessing pararenal and perirenal fat by renal imaging and the association with kidney function

Study	Renal imaging technique	Study design and population	Renal outcomes
Sun et al.[94]	PUFT	Cross-sectional study including 67 patients with obesity but no hypertension or T2DM, and 34 age- and sex-matched healthy volunteers	ACR and PUFT were higher in patients with obesity. PUFT was higher in patients with obesity with microalbuminuria compared with patients with obesity and normoalbuminuria; positive association between ACR and PUFT in the correlation and regression analysis. No correlation with eGFR (MDRD)
Geraci et al.[95]	PUFT	Cross-sectional study including 296 patients with hypertension	PUFT correlated negatively with eGFR (CKD-EPI). This association was also held in multivariate analyses
Lamacchia et al.[96]	PUFT	Cross-sectional study performed in 151 patients with T2DM	PUFT was an independent predictor of eGFR (CKD-EPI and MDRD) (negative association) and RI (positive association), but not of ACR
Shen et al.[97]	PUFT	Cross-sectional study including 89 patients with T2DM divided into those with (66) and without (23) albuminuria	PUFT was positively associated with albuminuria in multiple logistic regression analysis and linear regression analysis
Foster et al.[102]	RSF quantification (MDCT)	Cross-sectional design including 2923 participants: fatty kidney ($n = 879$), no fatty kidney ($n = 2044$). High renal sinus fat defined as "fatty kidney"	Fatty kidney was associated with a higher OR for CKD (cystatin C –eGFR) after the multivariable adjustment; fatty kidney was associated with an increased OR of microalbuminuria that was not statistically significant after multivariable adjustment
Wagner et al.[104]	RSF quantification (MRI)	Cross-sectional study with 146 patients at high risk for T2DM	RSF was independently associated with exercise-induced albuminuria
Spit et al.[105]	RSF quantification (MRI)	Cross-sectional study including 51 patients with T2DM	RSF correlated negatively with GFR measured by inulin clearance and effective renal plasma flow and positively with effective renal vascular resistance, even after adjustment
Zelicha et al.[106]	RSF quantification (MRI)	18-month randomized weight loss trial including 278 participants with abdominal obesity/dyslipidemia randomized to low fat- or Mediterranean/low carbohydrate diets	Higher RSF was associated with lower eGFR and higher albuminuria, even after adjusting for body weight Weight loss and RSF reduction was similar between groups Reduction in RSF was associated with ACR but not with eGFR (no significant differences after adjusting for weight and visceral fat loss)

Abbreviations: ACR, albumin/creatinine ratio; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDCT, Multi-detector Computed Tomography; MDRD, Modification of Diet in Renal Disease; MRI, magnetic resonance imaging; OR, odds ratio; PUFT, Pararenal and Perirenal ultrasonographic fat thickness; RI, resistance index; RSF, renal sinus fat; T2DM, type 2 diabetes mellitus.

renal perfusion and cortical microcirculation changes in the early stages of nephropathy.[92,93]

Pararenal and perirenal ultrasonographic fat thickness (PUFT) may be a useful tool to measure total visceral fat depots, correlating with visceral fat better than anthropometric parameters, and could be an independent predictor of renal impairment (Table 2). Although few studies have assessed the impact of PUFT on kidney function in subjects with obesity without other comorbidities, PUFT has been shown to be independently associated with renal injury after adjusting for traditional risk factors.[94–97] However, it is important to bear in mind that the nature of the link between fat depots and renal dysfunction and damage remains hypothetical, as most of the results available are derived from cross-sectional studies.

Ultrasound elastography is a non-invasive imaging technique that can assess tissue stiffness or elasticity via measuring its distortion in response to gentle pressure. It can be classified into two principal categories: quasi-static and dynamic elastography.[98] Ultrasound elastography has been widely used in the diagnosis of liver fibrosis, but its clinical application has also extended to the kidney to detect renal graft interstitial fibrosis as a long-term complication of renal transplantation.[99] As renal fibrosis correlates well with kidney function, ultrasound elastography could be an interesting alternative to renal biopsy, an invasive procedure with potential complications.[88] This technique has been previously used in patients with diabetic kidney disease (DKD) and permits the identification of early stages of the disease, including hyperfiltration without albuminuria.[100] Given the pathogenic similarities between DKD and ORG, ultrasound elastography appears to be a promising option to detect early changes in obesity-related kidney disease, but dedicated studies are needed to evaluate its usefulness in ORG.

4.4.2 | Computed tomography (CT)

CT permits a precise non-invasive high-quality evaluation of the kidney structure and function, allowing the assessment of ectopic adipose tissue depots associated with ORG, by measuring the density of the adipose tissue in Hounsfield Units.[101]

Specifically, renal sinus fat (RSF), as part of the perirenal adipose tissue, has been used in imaging studies to evaluate its association with kidney dysfunction. Therefore, in the Framingham study, CT-measured RSF was associated with impaired kidney function independently of intra-abdominal adiposity. Interestingly, the cohort prevalence of high RSF, defined using sex-specific percentiles for healthy subjects, was 30.1%, and these subjects had a higher odds ratio for hypertension and CKD (diagnosed as cystatin C-eGFR) after adjustment for BMI and abdominal visceral adipose tissue.[102]

4.4.3 | Magnetic resonance imaging (MRI)

MRI is another useful technique to quantify both the intrarenal and perirenal fat content of the kidney and, compared with CT, it has the advantage of not producing ionizing radiation, although its cost is generally higher.[103]

MRI has been used to evaluate the association between RSF and renal dysfunction.[104–106] Also, the lipid content of kidney tissue can be accurately assessed with proton magnetic resonance spectroscopy (^{1}H-MRS), offering a strong correlation with biopsy.[107,108] ^{1}H-MRS has shown that intrarenal lipid accumulation compromises renal oxygenation and promotes hypoxia; therefore, it might be an accurate indicator of early renal impairment in ORG.[109]

5 | ORG TREATMENT: PAST, PRESENT, AND FUTURE

5.1 | Weight loss

Because ORG is due to excess body fat, weight loss represents a logical therapeutic option. In this regard, observational studies and small prospective randomized trials have shown that weight loss is associated with a significant reduction in proteinuria and a reduced decrease in eGFR. However, the majority of studies conducted to date have been non-controlled and non-randomized studies undertaken in patients with DKD and obesity.[110–112]

Important evidence emerges from the evolution of patients with morbid obesity undergoing bariatric surgery. Observational studies and randomized controlled trials have shown that bariatric surgery (and subsequent weight loss) is associated with a significant reduction in albuminuria and renal function stabilization/improvement in patients with or without established CKD.[113–115] In addition, glomerular hyperfiltration improves after bariatric surgery, suggesting that glomerular dysfunction can be reversed in individuals without apparent renal disease.[113] These results are more pronounced after bariatric surgery as compared with lifestyle modifications, probably due to the more pronounced effect and long-term maintenance of weight loss induced by bariatric surgery.[113,114,116] Indeed, weight loss after BS induces a decrease in adipokines and pro-inflammatory and pro-fibrotic factors associated with kidney damage.[117] Therefore, drastic weight reduction through bariatric surgery could be considered an excellent multi-targeted therapy in patients with extreme obesity and CKD.[117]

5.2 | RAAS blockade

Given that RAAS plays a central role in the pathophysiology of ORG, another effective therapeutic approach in these patients is RAAS blockade with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II type I receptor blockers (ARBs). This pharmacological blockade confers reno-protective effects, by reducing hyperfiltration and proteinuria, and delays the progression to ESRD.[118,119]

It is noteworthy that, although clinical trials specifically conducted in subjects with obesity but no diabetes are limited, some studies reveal that the antiproteinuric and reno-protective effects of RAAS

blockade might be even greater in this population.[120,121] Therefore, in a post hoc analysis of the Ramipril Efficacy In Nephropathy (REIN) trial, the effect of ramipril was higher among subjects with obesity than in individuals who did not have obesity, noting a maximum antiproteinuric effect and marked attenuation of the risk of ESRD in patients with obesity.[120] This effect has also been shown in small clinical trials and observational studies.[63,121]

On the other hand, although a dual blockade combining an ACEI with an ARB is currently discouraged owing to a more deleterious safety profile,[122] Morales et al. have shown that the addition of the mineralocorticoid-receptor antagonist (MRA) spironolactone might confer supplementary renal benefits in patients with obesity and proteinuria treated with ACEIs or ARBs.[28] The selective MRA finerenone has also recently been shown to prevent CKD progression and reduce cardiovascular events in subjects with T2DM and CKD.[123] Further research, however, is needed to elucidate the effect of this drug on individuals with CKD without diabetes.

Finally, the clinical benefit of RAAS blockade in patients with obesity but without proteinuria who are at high risk of developing CKD remains unknown, although the recently developed PRIORITY trial revealed in a secondary endpoint that spironolactone did not prevent progression to albuminuria in high-risk patients classified by CKD273.[85]

5.3 | Sodium-glucose cotransporter 2 inhibitors (SGLT2i)

SGLT2i are a new therapeutic class of antidiabetic drugs that have been associated with a reduction in renal events (progression of renal disease, proteinuria, and death from renal cause) in patients with T2DM and obesity.[124] In a randomized controlled clinical trial done in patients with advanced DKD, canagliflozin significantly lowered the rate of adverse renal outcomes (doubling of serum creatinine, end-stage renal disease and death from renal, or cardiovascular cause) by more than 30%.[125]

More recently, the large-scale, long-term outcome trial DAPA-CKD, which included more than 4000 patients with CKD with and without diabetes, showed that dapagliflozin reduced the risk of kidney failure, regardless of the presence or absence of diabetes (primary composite endpoint: >50% sustained decline in eGFR or reaching ESRD or cardiovascular death or renal death).[126] Additional evidence will be offered by the ongoing large-scale, long-term outcome trial EMPA-KIDNEY that includes patients with obesity and no diabetes mellitus (NCT03594110). Table 3 summarizes the studies evaluating SGLT2i treatment in subjects with obesity and no diabetes mellitus.

It is important to highlight the similarity in the pathogenesis of obesity-induced renal damage and diabetes-induced renal damage.

TABLE 3 Renal outcomes of sodium–glucose cotransporter 2 inhibitors (SGLT2i) in clinical trials including participants with obesity and no diabetes mellitus[a]

Study	SGLT2i	Study design	Renal outcomes
Heerspink et al.[126] ($n = 4304$) (treatment period: 2.4 years)	Dapagliflozin	Patients with/without T2DM (eGFR 25–75 ml/min/1.73 m^2; ACR ≥ 200 and ≤5000 mg/g) randomized 1:1 to either dapagliflozin or placebo	Dapagliflozin reduces the risk of kidney failure – primary composite endpoint: ≥50% sustained decline in eGFR or reaching ESRD or CV death or renal death
EMPA-KIDNEY (NCT03594110) ($n = 6000$) (treatment period: 3.1 years)	Empagliflozin	Patients with/without T2DM (eGFR 20–45 ml/min/1.73 m^2 or 45–90 ml/min/1.73 m^2 with ACR ≥ 200 mg/g) randomized 1:1 to either empagliflozin or placebo	Composite primary outcome: time to first occurrence of kidney disease progression (defined as ESRD, a sustained decline in eGFR to <10 ml/min/1.73 m^2, renal death, or a sustained decline of ≥40% in eGFR from randomization) or CV death. Estimated study completion date: 2022
EMPATHY (NCT04143581) ($n = 44$) (treatment period: 1 month)	Empagliflozin	Participants with obesity/metabolic syndrome without T2DM (eGFR >60 ml/min/1.73 m^2). Single group assignment of empagliflozin	Primary outcome: measured eGFR. Estimated study completion date: 2022[b]
REGROUP (NCT04243850) ($n = 72$) (treatment period: 7 days)	Empagliflozin	Patients with/without T2DM (BMI > 25) with either preserved or impaired kidney function without macroalbuminuria. Crossover assignment of empagliflozin/placebo	Primary outcome: measured eGFR. Estimated study completion date: 2022

Abbreviations: SGLT2i, sodium-glucose cotransporter 2 inhibitors; eGFR, estimated glomerular filtration rate; ACR, albumin/creatinine ratio; ESRD, end-stage renal disease; CV, cardiovascular; BMI, body mass index; T2DM, type 2 diabetes mellitus.

[a]Data from ongoing clinical trials were obtained from ClinicalTrials.gov (last accessed December 21, 2021). Only studies with primary renal outcomes were included. Studies including only participants with obesity with demonstrated glomerulopathy different from ORG were excluded.

[b]Withdrawn (lack of funds).

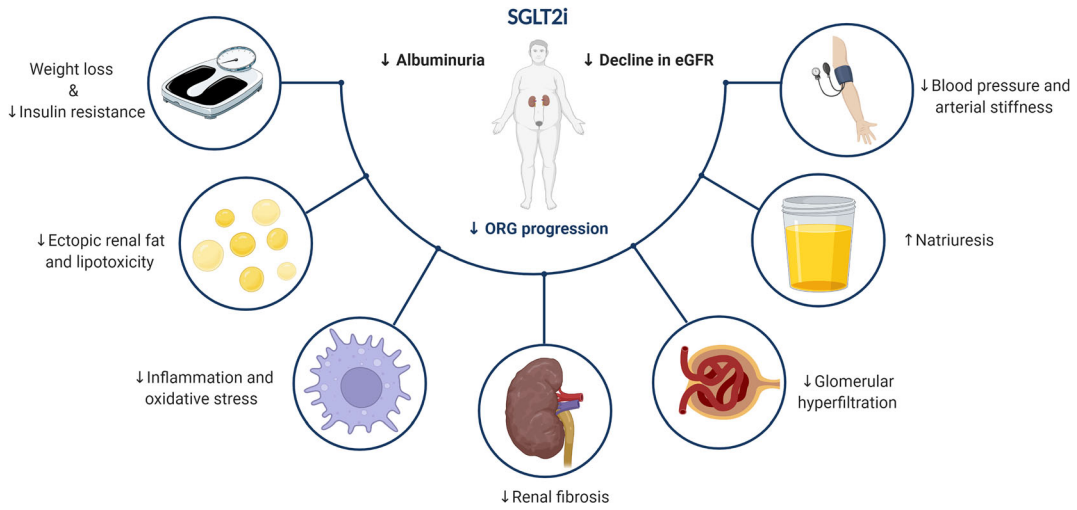

FIGURE 3 Potential mechanisms explaining the effect of sodium-glucose cotransporter 2 inhibitors (SGLT2i) on ameliorating the progression of obesity-related glomerulopathy (ORG). eGFR, estimated glomerular filtration rate

Along with hyperglycemia in patients with diabetes mellitus, in both conditions the fundamental pathogenic mechanism is glomerular hyperfiltration.[60] Specifically, in patients with ORG there is an increase in tubular sodium reabsorption in the loop of Henle, with the macula densa receiving less sodium, leading to afferent arteriole vasodilation and an increase in intraglomerular pressure.[20] Therefore, since SGLT2i decrease sodium and glucose reabsorption and increase sodium delivery to the macula densa (inducing afferent arteriole vasoconstriction and counteracting glomerular hyperfiltration), these drugs could have potential benefits in non-diabetic kidney disease, and specifically in ORG, reducing albuminuria and slowing the decline in eGFR. Also, parallel to their hemodynamic effects, the weight loss properties of SGLT2i might also contribute to attenuate renal injury[127] and could even have a role in ectopic renal fat reduction as shown in other organs.[128,129] Moreover, the blood pressure-lowering effects of SGLT2i could reduce intraglomerular pressure that damages the glomerular filtration barrier. Finally, another potential effect of SGLT2i is the improvement of glomerular changes and renal injury by reducing the release of pro-inflammatory cytokines and oxidative stress.[130] Figure 3 displays the potential mechanisms that could help explain the reno-protective effects of SGLT2i in ORG beyond their glucose-lowering properties.

5.4 | Other targets

Alternative classes of antidiabetic drugs could be effective in ORG as several preclinical studies have demonstrated.[131–134] Therefore, the pleiotropic effects of metformin beyond glucose-lowering activity have been reported in animal models, revealing positive actions on the kidney in the context of both DKD and different types of renal diseases.[131] Metformin acts as an activator of AMPK, restores normal podocalyxin expression and limits its urinary excretion, modulates podocyte apoptosis, reduces pro-inflammatory cytokine release and fibrosis, and diminishes lipid deposition.[131]

On the other hand, a meta-analysis of 15 randomized controlled trials observed that thiazolidinedione treatment in patients with diabetes and normoalbuminuria/microalbuminuria was associated with decreased urinary albumin excretion, and also with reduced urinary protein excretion in patients with proteinuria.[135] Direct actions of thiazolidinediones on PPARγ receptors and other alternative pathways promote insulin-sensitivity, trigger anti-inflammatory and anti-proliferative mechanisms, antagonize the RAAS, prevent lipid accumulation, and improve endothelial function.[136]

Incretin-based therapies—dipeptidyl peptidase 4 inhibitors (DPP4i) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs)—increase insulin release from the pancreas and favor insulin sensitivity. DPP4i prevent the cleavage of multiple beneficial peptides, resulting in decreased RAAS and sympathetic activity, inflammation, and fibrosis.[137] GLP-1 RAs promote natriuresis by inhibiting proximal tubular Na/H exchanger 3, reduce the activation of RAAS and have direct anti-inflammatory and anti-fibrotic effects on the kidney.[137,138] GLP-1 RAs are also associated with relevant and sustained weight loss, both in subjects with and without T2DM,[139–141] thereby making these drugs very attractive for the treatment of ORG. However, no GLP-1 RAs trials assessing primary renal outcomes have yet been published, although secondary endpoints and post hoc analyses presented in cardiovascular trials have shown promising results.[141–143] In this regard, the ongoing clinical trial FLOW is currently assessing the impact of semaglutide on renal outcomes. This trial plans to include more than 3000 participants with moderate-to-severe DKD, who will be randomly assigned to receive semaglutide or placebo for up to 5 years. The primary outcome will be a composite of persistent eGFR decline ≥50%, incident ESRD, death from kidney disease or death from cardiovascular disease (NCT03819153).

Finally, other promising agents that have shown a great potential in weight loss reduction are tirzepatide (a dual glucose-dependent insulinotropic polypeptide and GLP-1 RA), or cagrilintide, a long-acting amylin analogue. Therefore, both drugs could constitute potential

therapeutic options for patients with ORG, but devoted clinical trials are needed.[144,145]

6 | CONCLUSIONS

A parallel increase in the prevalence of ORG is foreseen with the increasing global obesity epidemic. Accordingly, important health consequences may be expected, given the association between ORG and CKD, ESRD and increased mortality. The underlying mechanisms for the development of ORG are complex and not yet fully understood, although increasing evidence confirms that they can induce kidney damage regardless of the presence of traditional kidney aggressors in obesity, such as hypertension and T2DM.

Future perspectives in this area include the proteomic characterization of the disease by defining specific urinary peptide patterns. In addition, new biomarkers for the diagnosis of kidney injury in the early stages might be useful for the evaluation of ORG, although further research is needed before these experimental models can be included in clinical practice. Similarly, renal imaging could facilitate the identification and follow-up of high-risk patients; however, it must be confirmed in longitudinal studies.

Therapeutic measures to reduce proteinuria, such as weight loss and RAAS blockade, delay the progression to ESRD and are the current treatment for ORG. In addition, certain glucose-lowering agents, such as SGLT2i and GLP-1 RAs, could become potential therapeutic strategies for this condition. Large-scale trials with SGLT2i conducted in subjects with and without T2DM have been shown to reduce the risk of renal events. Moreover, GLP-1 RAs exert pronounced weight reduction effects, thus potentially having a key impact on ORG. However, only forthcoming dedicated clinical trials will be able to demonstrate whether all these drugs are effective in subjects with ORG.

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CONFLICT OF INTERESTS

The authors have nothing to disclose.

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