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Obesity-related glomerulopathy in children: connecting pathophysiology to clinical care

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ABSTRACT

Obesity has continued to emerge as a worldwide pandemic and has been associated with a significant increase in associated comorbidities. These include well-known conditions such as hypertension and diabetes, as well as lesser-known conditions such as obesity-related glomerulopathy (ORG). The main etiology of ORG is podocyte damage, but contributing theories include dysfunctional renin–angiotensin–aldosterone system activation, hyperinsulinemia and lipid deposition. Recent advances have made strides in understanding the complex pathophysiology of ORG. The key to treating ORG is weight loss and proteinuria reduction. Lifestyle modification, pharmacological interventions and surgery are mainstays of management. A special focus on obese children is required, as childhood obesity tracks into adulthood and primary prevention is key. In this review we discuss the pathogenesis, clinical features and established and newer treatment modalities of ORG.

Keywords: children, obesity, obesity-related glomerulopathy, ORG

INTRODUCTION

In the past few decades, obesity has emerged as a global pandemic, with an estimated 51% of the population projected to be obese by 2030. Obesity is defined as a body mass index (BMI) $\geq$30 kg/m^2 in adults. In children, the BMI distributional approach is used, defining children above the 95th percentile of age- and gender-specific percentiles as obese [1]. In the USA, the Centers for Disease Control (CDC) formulated BMI growth charts for children from the data collected from numerous studies from 1963 to 1994 [2]. In the last 3 decades, the prevalence of childhood and adult obesity has increased by 47.1% and 27.5%, respectively [3]. The prevalence of obesity in children and adolescents has increased 3-fold, with lifestyle choices and environmental changes being the main driver in bringing about this change [4]. Obesity increases the risk of cardiovascular and metabolic comorbidities such as hypertension, diabetes mellitus type 2, chronic kidney disease (CKD) and metabolic syndrome.

Obesity is a challenging issue in the pediatric population, as many children continue to be obese in adulthood too. Obese children are at an increased risk of developing CKD or end-stage renal disease (ESRD) than children with a normal BMI [5]. Such individuals may develop a pathological syndrome known as obesity-related glomerulopathy (ORG) [6]. In the last 3 decades

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there has been a 10-fold increase in the incidence of ORG. Morphologically, ORG can be described as glomerulomegaly and focal segmental glomerulosclerosis (FSGS). Glomerulomegaly in these patients is a consequence of hyperfiltration [7]. The histological changes on renal biopsies of patients show podocyte hypertrophy, reduced podocyte density and mesangial cell proliferation. ORG is also described as secondary FSGS [8]. Currently the diagnosis of ORG must meet the following criteria: (i) The body mass index (BMI) must be >30 kg/m^2. This excludes the obesity caused by any endocrine causes or obesity and diabetes induced due to drugs. (ii) Proteinuria is present without gross hematuria or significant microscopic hematuria. (iii) Pathological changes in the renal tissue are observed, such as glomerular hypertrophy, which may be FSGS. This also includes immunofluorescence staining of the renal tissue showing C3 or immunoglobulin M deposits. (iv) Patients with renal diseases of primary origin such as glomerular nephropathy or immunoglobulin A nephropathy must be excluded [9]. Weight loss has been shown to cause significant improvement in patients with proteinuria. However, it cannot be linked to enhancement of renal function since a notable deterioration of glomerular sclerosis was still observed in a child.

Pathophysiology

Hemodynamic Changes

The role of hyperfiltration in ORG has become increasingly important to understand. One such cause of hyperfiltration can be attributed to hypertension, which causes capillary wall stress, basement membrane expansion and glomerulomegaly [10]. In the last 3 decades, the prevalence of childhood and adult obesity has increased by 47.1% and 27.5%, respectively [3]. Kidney hemodynamics, measured by glomerular filtration rate (GFR), renal plasma flow (RPF) and filtration fraction (FF), have been shown to be higher in obese individuals when compared with their lean counterparts [11]. More specifically, renal vasodilation and RPF increase in the afferent arteriole. The increase in GFR is attributed to the increased difference in transcapillary hydraulic pressure [11]. Renal injury and GFR decline can also be due to increased tubular sodium resorption as a response to volume depletion. As glucose and sodium are reabsorbed via sodium–glucose cotransporter 2 and 1 (SGLT2 and SGLT1) receptors, the decrease in sodium triggers tubuloglomerular feedback, thus causing preglomerular vasodilation and an increase in GFR. The net result is hyperfiltration [12]. As such, therapies that inhibit SGLT receptors can reverse hyperfiltration, one of the central drivers of damage in this disease process.

Obesity, RAAS and ORG

A study by Cassis *et al.* [13] demonstrated an increase in the expression of renin, angiotensin-converting enzyme (ACE), angiotensin II and angiotensin II type 1 and 2 receptors. Activation of the renin–angiotensin–aldosterone system (RAAS) is common in obesity and is responsible for inducing significant kidney damage [14]. As per the study in rodent models by Massiera *et al.* [15], 30% of the circulating angiotensinogen is produced by the adipocytes. RAAS activation along with increased sympathetic activity lead to increased natriuresis and renal tubular resorption of sodium. This results in volume expansion in the system that further augments kidney damage [16]. Angiotensin and aldosterone both have a predominant vasoconstrictive effect. This results in the increased hydrostatic glomerular pressure in the efferent arteriole [17]. Increased aldosterone stimulation causes activation of the epithelial sodium channel (ENaC) along with transforming growth factor (TGF) suppression. This collectively results in hyperfiltration and contributes to kidney injury [18].

Adipose tissue and ORG

Adipose tissue provides and stores energy while regulating metabolism in the body. There are inflammatory mediators released by adipose tissue that led to ORG. In the event of local inflammation, the kidney releases adipokines such as adiponectin, leptin, tumor necrosis factor (TNF)-α, interleukin-6 (IL-6) and other inflammatory medicators. Also, there is mobilization of cells like leukocytes, macrophages and fibroblasts [19]. The resulting inflammation all contribute to worsening renal function via glomerulosclerosis, renal fibrosis and proteinuria.

Podocyte injury and ORG

The histopathological hallmark of ORG is podocyte injury. Podocytes are the main unit of filtration in the glomerulus and are damaged by adipokines and the RAAS. Angiotensin II acts on podocytes, causing them to release intracellular calcium stores. Increased cytosolic calcium activates chloride channels in podocytes, thereby depolarizing them [20]. Inflammatory processes cause podocyte foot process widening, detachment of podocytes from the basement membrane and a reduction in their total number. Damage to the podocytes is irreparable. The chances of recovery are limited since podocytes have little capacity to regenerate [21].

Insulin resistance

Hyperinsulinemia causes hyperfiltration in the kidneys. Insulin resistance gives rise to endothelial damage and increases the permeability of vascular structures. It also causes hyperplasia of the mesangium and retention of salt in the body through the distal tubule ENaCs [22]. Insulin is also responsible for increasing GFR, due to a vasodilatory effect or via its ability to cause sodium retention. In patients with type 2 diabetes, hyperinsulinemia is associated with an increase in the urine albumin excretion rate, with little or no effect on systemic albumin permeability [22]. Hyperinsulinemia is also responsible for hypertension related to increased activation of the RAAS. Insulin accentuates the effects of angiotensin II on mesangial cells, thus worsening hypertension, intraglomerular pressure, proteinuria and inflammatory cytokines (TNF-α, IL-6) and growth factors (insulin-like growth factor 1, TGF-1). The severity of insulin resistance is associated with oxidative stress, which further contributes to renal injury.

Mitochondrial damage

The kidney acquires its energy from mitochondrial beta oxidation of fatty acids. There is deposition of lipids in the renal tissue, thus impairing its energy uptake. Reactive oxygen species are generated due to mitochondrial dysfunction, causing massive podocyte apoptosis [23]. FSGS is known to be a fundamental lesion in the pathogenesis of obesity-related glomerulopathy. Once a patient develops FSGS, the progression to ESRD is rapid. Fig. 1 presents a summary of the pathophysiologic mechanisms leading up to ORG.

Risk factors

Obesity in children is a major health crisis. It is a complex entity that is affected by various factors such as nutrition, physical

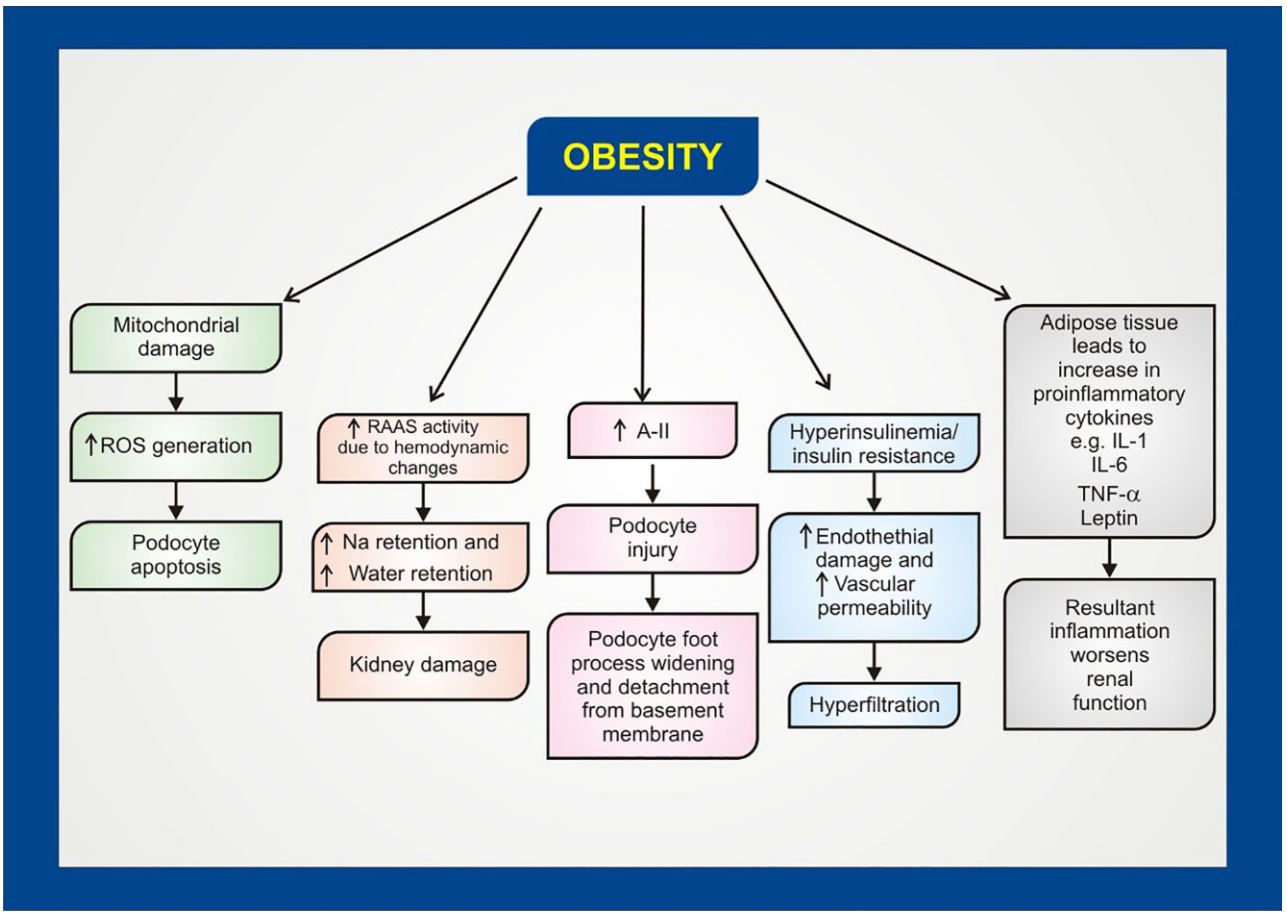

Figure 1: The pathophysiology of obesity-related glomerulopathy. These are some of the numerous mechanisms through which obesity can lead to decline in the renal function. With time, constant damage to the renal tissue leads to changes such as FSGS, scarring and permanent damage. ROS: reactive oxygen species; A-II: angiotensin II.

activity, ethnicity, environment, genetics and socioeconomic status [24]. Several dietary practices, such as high consumption of high caloric foods, sugary beverages and fast food, can contribute to obesity. Children who are born small- or large-for-gestational age or were exposed to maternal diabetes mellitus are prone to developing childhood obesity. Various ethnicities have different tendencies to develop obesity, including those of Hispanic, Aboriginal and South Asian ancestry. Urban areas have a higher percentage of obesity as compared with rural areas [25]. Pathological conditions such as Cushing syndrome, hypothyroidism and growth hormone resistance are also noted to contribute to childhood obesity. Metabolic syndrome is an important hormonal disorder that is implicated in obesity in children and young adolescents. Abdominal obesity, hyperglycemia, hypertension and dyslipidemia comprise metabolic syndrome, with obesity being the most observed feature. According to a study by Engin in 2017 [26], obesity prevalence was 31% and is expected to increase up to 53% by the year 2035. Sangun *et al.* [27] conducted a study in 2011 demonstrating that of 614 children, 307 male and 307 female (age 11.3 ± 2.5 years), metabolic syndrome was present in 39% and 33%, respectively. Genetic diseases like Prader–Willi syndrome and WAGR (Wilms tumor, aniridia, genitourinary anomaly, mental retardation) syndrome also cause obesity in children. Visceral fat obesity is also known to increase the risk of ORG. Although ORG is a renal pathology that develops secondary to obesity, visceral fat obesity can increase the chances of its manifestation [28]. Obesity-related pathologies such as sleep apnea, nonalcoholic fatty liver disease and pulmonary hypertension also increase a patient's risk of acquiring kidney damage.

Manifestations

The most common clinical presentation in ORG is proteinuria. In most cases the proteinuria is in the subnephrotic range (3.5 g/day). ORG is distinctly different from nephrotic syndrome because it lacks characteristic edema, hypoalbuminemia and hyperlipidemia [29]. The proteinuria is persistent for years, with a gradual increase in many patients. This change may go undetected for a long time. In a study by Praga *et al.* [30], it was determined that ≈10–30% of patients with ORG develop ESRD. ORG-related FSGS has a slower progression, subnephrotic proteinuria and irregular effacement of podocytes. In 2013, Tsuboi *et al.* [31] observed 28 patients with ORG. After a 2-year follow-up, 7 of 20 patients (35%) had a 50% increase in serum creatinine and 2 patients (10%) showed a 100% increase in creatinine and eventually developed ESRD. Obesity brings about physiological changes such as increased cardiac output to compensate for extra blood flowing to the adipose tissue and in turn increasing the fluid to kidneys, lungs, skeletal muscle etc.

Table 1: Clinical presentation in ORG studies.

Author, year	Subjects, *n*	Proteinuria	Microalbuminuria	Elevated serum creatinine	CKD	Kidney failure
Chagnac *et al.*, 2003 [60]	8	–	Present	–	–	
Navarro-Diaz *et al.*, 2006 [62]	61	Present	Present	–	–	
Schuster *et al.*, 2011 [64]	56	Present	–	Present	–	
Denic and Glassock, 2020 [6]	–	Present	–	–	–	
Wei *et al.*, 2021 [9]	–	Present	–	–	–	
Tsuboi *et al.*, 2017 [28]	–	Present	–	–	–	
Kambham *et al.*, 2001 [4]	71	Present in 40	–	–	–	
Praga *et al.*, 2001 [29]	15	Present in 6	–	–	–	
Tsuboi *et al.*, 2017 [28]	28	–	–	Present in 9	–	Occurred in 2
Xu *et al.*, 2017 [10]	–	Present	–	–	–	–
Medyńska *et al.*, 2021 [49]	–	–	Present	–	–	–
Herman-Edelstein *et al.*, 2021 [58]	–	–	Present	–	–	–
Shen *et al.*, 2010 [59]	–	Present	–	–	–	–
Abitbol And Rodriguez, 2009 [60]	–	Present	–	–	–	–
Yang *et al.*, 2020 [68]	20	–	–	Present in 7	–	Occurred in 2

In 1995, Ribstein *et al.* [32] performed a study to observe the effect of obesity on the kidney. Subjects with a BMI of 27–40 kg/m^2 with similar age, gender and blood pressure were studied. The GFR, RPF and FF were increased in these people. These maladaptive changes can lead to hyperfiltration. This study stated obesity amplifies the effects of hypertension on the kidney. These unfavorable changes due to obesity make the kidney more susceptible to injury. More recent studies further support that maladaptive changes contribute to hyperfiltration. Okabayashi *et al.* [30] demonstrated that single-nephron glomerular hyperfiltration occurs in patients with ORG and is a sign of early-stage ORG even if there is preserved renal function. Furthermore, the single-nephron GFR was inversely proportional to the CKD stage, suggesting that hyperfiltration underlies ORG. Table 1 shows clinical features seen in different studies of ORG. Also, in patients with ORG, the lack of therapeutic intervention results in residual proteinuria. The progression is typically slow paced or constant. However, some individuals can develop rapid deterioration and thereby develop renal failure and ESRD. Old age and higher creatinine levels are associated with a poorer prognosis, as well as averaged proteinuria during follow-ups [33]. Patients already suffering from a primary renal disease will have a poorer prognosis overall if additionally diagnosed with ORG [34].

Knowing that excess adipose tissue is related to kidney injury and the development of metabolic syndrome, clinicians have worked on therapy recommendations to address the risk factors and provide nonpharmacological treatments to slow the progression of CKD through improvements in diet and physical activity. The Pediatric Renal Nutrition Taskforce developed recommendations to address the factors that put children at risk for disease progression [35]. Metabolic syndrome is more common in children with CKD, thus the underlying circumstances that predispose individuals to metabolic syndrome must be addressed [36], and abdominal dominant adipose tissue deposition is a driving force for the development of metabolic syndrome. In the Pathobiological Determinants of Atherosclerosis in Youth Study, having cardiovascular risk factors predisposed patients to more atherosclerotic lesions in the coronary vessels [37]. While there is difficulty in determining the precise defining characteristics for metabolic syndrome, there is widespread consensus that metabolic syndrome and its sequelae are often partnered with declining renal function. It is important to note that BMI is not a criteria in defining metabolic syndrome, as patients with CKD present with more cardiovascular risk factors. Regardless, there is a correlation of the progression of CKD, death and renal transplant health with obesity.

Biomarkers

Biomarkers are essential to detect early signs of obesity-related glomerulopathy in pediatric and adult populations to prevent progression of the disease. The presence of albuminuria and proteinuria have been widely used as a noninvasive assessment of kidney function, however, their determination cannot always be used as a marker of early kidney damage. Therefore, in the recent years there have been numerous studies in the pursuit of markers that can be utilized for diagnosing early stages of kidney damage. The majority of these biomarkers still require proper assessment through well-designed studies. Some of the promising new biomarkers are urinary glutamyl aminopeptidase (GluAp), urinary podocalyxin (PCX), urinary kidney injury molecule-1 (KIM-1), alpha-1-acid glycoprotein (AGP), urinary N-acetyl-beta-D-glucosaminadase (NAG) and urinary neutrophil gelatinase-associated lipocalin (NGAL) [38, 39]. In the pediatric population, overexpression of theses biomarkers has been observed in patients with obesity [40, 41].

Additionally, some of these markers have been known to detect early stages of kidney damage in obese patients with diabetic nephropathy, such as urinary cystatin [39]. KIM-1 and urinary NGAL have been associated with a rapid decline in eGFR in such patients [42]. In a study conducted by Suwanpen *et al.* [43], PCX was elevated in patients with obesity compared with individuals without obesity, indicating tubular damage. Montoro-Molina *et al.* [44] conducted a study on Zucker obese rats in which GluAp was seen to be associated in early diagnosis of tubular damage in the subjects. Detectable levels of GluAp also indicated the presence of fibrosis in these subjects. Some new markers that detect specific early glomerular and podocyte changes are urinary podocin and nephrin [45–47]. In an independent cohort study conducted by Wendt *et al.* [48], a new marker called BMI150 was developed to detect ORG. This marker has 150 urinary peptides, all consisting of collagen. BMI150 has accurately identified patients as obese or nonobese with preserved kidney function. However, due to a small number of subjects, this marker could

Table 2: Biomarkers for detecting potential early kidney injury in ORG.

Tubular injury markers		Glomerular injury markers
Proximal tubule	Distal tubule	Cyst C
Cyst C	NAG	Podocin
NAG	NGAL	Nephrin
NGAL	GluAp	PCX
GluAp		GluAp

Cyst C: cystatin C.

not further identify patients with CKD. Table 2 summarizes the various biomarkers that help in the early detection of ORG.

Recent studies have indicated that AGP is a more reliable indicator than albuminuria to depict the permeability of the glomerular filtration barrier. AGP is an acute phase protein that has both pro- and anti-inflammatory actions. As a result, it affects the release and inhibition of cytokines like IL-6, IL-1 and TNF-α [49]. Medyńska *et al*. [50] did a study in 2021 to evaluate urinary AGP as a marker in obese children. The study group had 125 obese children, 8–17.9 years of age (mean 13.7 $\pm$ 2.84). The control group had 33 subjects. The study group was observed to have higher levels of AGP, with a mean of 578.5 $\pm$ 165.2 ng/mg, while the control group had levels of 447.9 $\pm$ 37.9 ng/mg. Therefore, increased levels of AGP suggest that it is a valuable biomarker of glomerular damage in obese children. However, while AGP demonstrates a positive correlation with glomerular injury, there were no significant differences in urinary AGP according to the degree of obesity. Podocyte damage is also indicated by the increased expression of podocin messenger RNA. This podocyte protein is a more specific and reliable marker than other proteins since its expression is enhanced when there is podocyte damage. Megalin, a renal tubular protein, has been shown to be a useful biomarker of ORG and renal injury in children [51]. At the moment, there are few human studies pertaining to the markers of early damage to the kidney. Although, these biomarkers offer vital insights into the early detection of kidney damage, there is a need for further research into their utility as early detectors of ORG.

Treatment

The management for ORG includes lifestyle changes as well as therapeutic drugs. Initial first-line therapy is weight loss, with an emphasis on a healthy diet and physical exercise. A comprehensive approach towards interventions for obesity and ORG is an integral part of management of this disease. There are multiple factors that can contribute to obesity in an individual, including genetic factors, race, psychosocial issues and social makeup. Along with these, a person's socioeconomic status also plays an integral role in their lifestyle choices. A family's feeding practices greatly influence a person's food behaviors. Any kind of weight-related bullying or stigma can push an individual into developing body image issues. There is a great need for society to step up and bring about changes that can curb obesity and its rise as a worldwide pandemic over the last 2 decades. Readily available fresh produce in accessible neighborhood markets will allow people to eat healthier. The media also has a role in promoting healthier lifestyle choices. Food marketing has a huge potential to reach large numbers of people and engage them in more proactive lifestyle choices. Local, state and national policies focusing on investment in agriculture, food availability and trade hold great importance in helping individuals achieve healthier options. Collectively these measures are imperative in keeping society healthy overall.

Weight loss has been proven to be directly proportional to a reduction in proteinuria. Clinically, proteinuria is the most common manifestation of ORG. Therefore, pharmaceuticals that help to reduce proteinuria are most used as treatment modalities in ORG. These therapies also help slow the progression of renal damage. Examples of such medications are ACE inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) or a combination of these the drugs. A study done by Praga *et al*. [30]. in 2001 observed that the use of ACEIs in patients with biopsy-proven ORG reduced proteinuria levels to 30–80% of baseline values. A greater reduction in proteinuria was seen in obese patients as compared with those with a BMI in the normal range.

Certain trials have also demonstrated an improvement in renal function when SGLT2 inhibitors or glucagon-like peptide agonists are used in patients undergoing weight loss [34]. Additionally, SGLT2 inhibitors are of the utmost importance, as they have been shown to decrease hyperfiltration. Cherney *et al*. [52] demonstrated that SGLT2 inhibition reduced GFR by 19% in patients with hyperfiltration. Furthermore, SGLT2 inhibition has been shown to maintain a reduction in GFR and albumin:creatinine ratios for up to 26 weeks [53]. SGLT2 inhibitors reduce sodium and glucose reabsorption along with increased sodium delivery to macula densa cells. This change induces afferent arteriole vasodilation and an increase in intraglomerular pressure [54]. These changes brought about by SGLT inhibitors benefit kidneys damaged by obesity. This also helps in reducing albuminuria, which is one of the most common manifestations of ORG. Along with this, there is an improvement in eGFR in patients as well [54]. SGLT inhibitors promote weight loss, which can have a favorable outcome in obese patients and helps them mitigate further kidney damage [55]. SGLT inhibitors also help in reducing the production of inflammatory mediators and curb oxidative damage [56].

Table 3 summarizes some therapeutic interventions for ORG based on pathophysiological mechanisms. Newer medications have been developed to target lipid metabolism and have shown promise in ORG therapy. Some of these new agents are sterol regulatory element-binding protein antagonists, farnesoid X receptor and Takeda G protein-coupled receptor 5 agonists, peroxisome proliferator-activated receptor α agonists and liver X receptor agonists. Additionally, treatment with the tetrapeptide SS-31 can overcome lipid toxicity in the kidney via mitochondrial protection [57]. Rimonabant, an anti-obesity medication, has shown beneficial effects in treating metabolic syndrome. Rimonabant also has a potential benefit in managing and treating ORG [58].

If patients are unable to lose weight through lifestyle modification, then bariatric surgery is recommended [59]. In a comparison between dietary modifications and bariatric surgery, it was found that patients undergoing surgery had more rapid weight transformation. Postsurgery, all patients consistently experienced normalization of GFR. In patients with comorbidities such as type 2 diabetes mellitus and hypertension, this adjustment of GFR also helped patients achieve favorable glycemic control and blood pressure [60]. In the pediatric population, more attention must be paid to lifestyle modification and healthier dietary practices. In postpubertal children, bariatric surgery can be considered [61]. A prospective study done by Chagnac *et al*. [62] in 2003 looked at eight obese patients. A reduction in renal blood flow, insulin and serum glucose was observed after surgery. In 2006, a study done by Navarro-Díaz *et al*. [63] consisting of 61

Table 3: Therapeutic interventions for ORG based on pathophysiological mechanisms.

Mechanism of renal damage	Intervention
RAAS pathway activation	ACEIs ARBs Aldosterone receptor blockers
Adipose tissue–mediated inflammatory mediators like adiponectin, leptin, IL-6, TNF-α	Weight loss Dietary modification (low potassium, Mediterranean, DASH, low sodium, decreased fast-food consumption) Steroids
Lipid deposition leading to mitochondrial damage	Weight loss Dietary modification Statin therapy Antioxidants Physical activity Improved sleep Decreased Psychosocial stressors Bariatric surgery

morbidly obese patients (BMI 53.62 ± 9.65 kg/m^2) noted a significant reduction in proteinuria, eGFR and microalbuminuria post-surgery. Serpa Neto *et al.* [64], in a retrospective study in 2009 on 140 morbidly obese patients with a BMI of 46.1 ± 5.4 kg/m^2, confirmed a reduction in BMI and proteinuria after bypass surgery. A study by Schuster *et al.* [65] in 2011 checked creatinine levels in 56 obese patients with baseline elevated creatinine after Roux-en-Y gastric bypass surgery. After the surgery, 76.7% patients had creatinine levels in the normal range. Thus bariatric surgery has been proven to achieve normal renal function.

Impact of obesity on transplanted patients

As per a study done by Ladhani *et al.* [66], obesity is associated with an increased risk of allograft failure in pediatric patients following a kidney transplant. In this study, 750 pediatric patients 2–18 years of age (median 12) were followed up for 10 years. Of these 750 children, 16.2% ($n = 102$) experienced acute graft rejection withing the first 6 months of the transplant, while 31.3% ($n = 235$) experienced allograft loss. At the time of transplantation, 17.2% ($n = 129$) of the children were overweight and 7.1% ($n = 61$) were obese. In children who have received a kidney transplant, obesity is frequently observed [67]. The reasons why obesity occurs in such settings are complex. In a study by Ho¨cker *et al.* [69], the reason for obesity was attributed to patients taking high-dose steroids, which have a stimulating effect on appetite.

CONCLUSION

With the increase in the global prevalence of obesity, there has been a parallel increase in the incidence of ORG, an important cause of CKD. There is a significant overlap between FSGS and ORG, therefore great clinical acumen from physicians is required to manage this condition efficiently with an accurate diagnosis and therapy. Emphasis should be focused on the prevention of obesity starting in childhood. Further research into the molecular mechanisms of ORG and newer therapies to halt and reverse progression are needed. Additionally, further research with longer durations and follow-up are needed. There are numerous ongoing studies in an effort to trace the unmet needs of research in terms of pediatric population data. The possible differences in adult and pediatric populations in terms of treatment modalities and their responses to therapies are a driving force for conducting more research in this field.

STATEMENT OF ETHICS

Since this article is a review article, there was no ethics approval or informed consent required. No study on human participants was performed in this review. The consent to publish is not applicable.

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AUTHORS' CONTRIBUTIONS

G.M. conducted the initial literature review. R.R. formulated the strategy for writing the article. R.R. and N.N. wrote and reviewed the manuscript. N.N. constructed the figure. O.B. and B.A. critically reviewed the manuscript. P.P. and S.B. edited the manuscript to ensure the final draft was suitable for submission.

DATA AVAILABILITY STATEMENT

There were no datasets generated or analyzed in this review article.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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