Obesity-related glomerulopathy (ORG) is a secondary form of glomerular disease that can occur in individuals with obesity. However, the absolute risk for an obese individual to develop progressive renal deterioration is low. Therefore, obesity alone appears to be insufficient to develop such severe renal injury, and there are likely other factors that contribute to the development of this entity. The glomerular hyperfiltration found in patients with ORG has been postulated to lead to structural

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abnormalities in glomeruli, such as glomerulomegaly and focal segmental glomerular sclerosis, in a manner analogous to that described in patients with reduced renal mass. In fact, recent studies suggest that a reduction in nephron mass is implicated in patients with ORG and synergistically contributes to the development of this renal complication together with obesity-induced changes in renal hemodynamics.

**INTRODUCTION**

Since the presence of proteinuria as a complication of massive obesity was first reported in 1974, several cases have been subsequently described [1–5]. Currently, this renal complication is known as obesity-related glomerulopathy (ORG) [6–9]. The mechanisms involved in the renal injury observed in patients with ORG are incompletely understood. However, a number of studies have consistently suggested the critical role of glomerular hyperfiltration, which is closely correlated with the marked glomerulomegaly and focal segmental glomerular sclerosis (FSGS) detected in the biopsies of ORG patients [6, 7, 10]. The increased incidence of ORG appears to be closely related to the epidemic of obesity in the general population. However, the absolute risk of progressive renal deterioration in any obese individual is low and only a minority of obese individuals develops this renal complication. Therefore, obesity appears to be insufficient to result in such severe renal injury, and there are likely other factors that contribute to the development of this entity.

**EPIDEMIOLOGY AND CLINICAL FEATURES OF ORG**

A report by Kambham et al. showed an increased incidence of ORG among kidney biopsy cases evaluated at Columbia University in the USA in recent decades [6]. A progressive increase in the number of biopsies identified as exhibiting ORG from 0.2% in 1986–1990 to 2.0% in 1996–2000 has been reported. Elsewhere, case series from Spain, China and Japan have raised alarm regarding the potential epidemic of this entity in accordance with the increased number of obese individuals in the general population worldwide [7–9].

In general, ORG is defined as a proteinuric renal disease in patients with a body mass index (BMI) of 30 kg/m² or more and the absence of other known renal diseases both clinically and histopathologically [6, 7, 9]. Therefore, when diagnosing this entity, it is crucial to exclude diseases that are closely related to obesity, such as diabetic glomerulosclerosis. The typical clinical features of ORG include moderate or massive amounts of proteinuria without a decrease in the serum albumin level [11]. This clinical characteristic is very useful for distinguishing these patients from those with idiopathic FSGS, in which complete nephritic syndrome often accompanies the presence of nephritic-range proteinuria. The reasons for the absence of complete nephritic syndrome in patients with ORG remain unknown; however, they may be associated with the different tubular management of filtered proteins and a very slow increase in urinary protein excretion. Although the long-term renal outcomes of ORG have been shown to be better than those of primary FSGS, a significant number of ORG patients ultimately develop end-stage renal disease [6, 7, 9].

Weight loss is a logical therapeutic approach to treating this entity. In fact, weight loss has been shown to be associated with significant reductions in urinary protein excretion in ORG patients [12–14]. However, clinically available information about this issue, especially observations with a long-term follow-up, is scarce. In our ORG patients, the time-averaged BMI significantly decreased compared with that observed at the time of biopsy [9]. However, our results showed that neither the BMI at the time of diagnosis or during the follow-up nor the rate of BMI changes during the follow-up exhibit relationships with disease progression.

**HISTOPATHOLOGY IN PATIENTS WITH ORG**

Previous reports have consistently identified glomerulomegaly and focal segmental glomerulosclerosis to be characteristic histopathologic findings in patients with ORG [6, 7]. ORG can be distinguished from primary FSGS histopathologically [6, 10]. For example, among the FSGS variants, the perihilar variant, a known form of FSGS that is typically induced by hemodynamic stress, is often found in patients with ORG, and foot process effacement is less prominent in ORG patients than in patients with idiopathic FSGS [6].

Although the origin of glomerulomegaly in patients with ORG is still incompletely understood, some plausible explanations for this typical morphological feature of ORG have been suggested. First, increased sympathetic nerve activity and/or systemic blood pressure induced by obesity may be a major factor. In fact, a significantly high rate of patients with ORG has been shown to have systemic hypertension [6–9]. Second is intraglomerular hypertension, which is mediated by vasodilation of the afferent arterioles [15]. The cause of this hemodynamic change is explained by an increase in salt reabsorption, which leads to an increase in the glomerular filtration rate through tubuloglomerular feedback. Although the mechanisms underlying this increase in salt reabsorption in the tubules remain unclear, the roles of several factors, including activation of the renin-angiotensin system, have been described [16]. Contraction of the glomerular efferent arteries is also involved in increased intraglomerular pressure, which leads to a decrease in the downstream peritubular capillary blood flow and induces ischemic renal injury [17, 18]. Third, the increased secretion of angiogenesis-promoting factors, including vascular endothelial growth factor, has been reported in tissue microarray analyses of renal biopsies in ORG patients [19]. Similar histological changes were found in a rat nephrectomy model in which increased glomerular tuft volume was shown to be related to increased numbers of glomerular capillaries [20]. Consequently, such angiogenic factors are secreted to increase the glomerular capillary number and glomerular capillary surface area. In other words, these histopathologic changes are essentially directed to those consistent with functional compensation of glomerular filtration. Therefore, it is
reasonable to consider that proteinuria and FSGS lesions occur in the glomeruli of ORG patients as a result of a compensatory failure in the preservation of the optimal surface area of the glomerular capillaries.

**BODY MASS EFFECTS ON REDUCED NEPHRON MASS**

It is known that the experimental ablation of 5/6 parts of rat kidneys results in progressive histological and functional deterioration of the remnant kidneys [21, 22]. In this animal model, the remnant glomeruli are markedly enlarged, followed by the induction of segmental and global glomerulosclerosis. The enlarged glomeruli found in this model have been shown to have a close relationship with intraglomerular hyperfiltration/hypertension. In addition, the progressive deterioration of renal disease observed in this model is effectively inhibited by treatment with angiotensin-converting enzyme inhibitors. Importantly, all of these features are quite similar to those typically observed in ORG patients. Therefore, it has been postulated that relative reductions in the number of nephrons as a result of increases in body size are implicated in the pathogenesis of ORG [23].

An experimentally decreased nephron mass state is clinically analogous to that of congenital renal agenesis or nephrectomy. According to a report describing a case series of ORG patients with FSGS, 8 of 15 ORG patients exhibited features indicating an apparent reduction in the number of nephrons, such as unilateral renal agenesis [7]. Although most patients with congenital renal agenesis and those who have undergone uninephrectomy actually do not develop urine abnormalities or renal impairment for several years, some of these patients do develop proteinuria and progressive renal dysfunction. The reason why most patients tolerate extensive reduction in renal mass without displaying any signs of renal damage, whereas others exhibit progression to renal failure is unknown. Praga et al. [24] reported that obese patients are at risk of developing proteinuria following unilateral nephrectomy. In that study, BMI was significantly higher in patients who developed slowly progressive proteinuria and renal insufficiency, in comparison with that observed in patients who did not exhibit these abnormalities. Furthermore, a study by the same group showed that obesity is an independent factor associated with the development of proteinuria or renal impairment among patients with congenital renal agenesis and remnant kidney [25]. These results suggest that obesity is a plausible factor that participates in the development of renal injury under conditions of severe renal mass reduction. In addition, these results suggest that not only obesity-induced relative reduction, but also absolute decreases in the number of nephrons are implicated in the development of renal injury associated with obesity, including ORG.

Recently, Fukuda et al. [26] reported the findings of a study using a rat uninephrectomy model in which body weight gain-induced hypertrophy of glomerular podocytes was specifically inhibited by genetic manipulation. In this animal model, the authors showed increases in the incidence of FSGS and urine protein excretion following the podocyte-specific inhibition of cellular hypertrophic changes. This interesting experimental study demonstrated that hypertrophy of the glomerular podocytes plays a role in the compensation of obesity-related glomerular injury. These findings suggest that the appearance of FSGS depends not only on obesity-related increases in glomerular tuft volume, but also on podocyte hypertrophic responses. Consistent with these findings, it has been reported that a relative reduction in the coating area of glomerular podocytes on the glomerular surface is in fact found in ORG patients [27]. The compensatory failure observed in ORG patients may therefore be additionally explained by a functional adaptation failure in glomerular podocytes.

**LOW GLOMERULAR DENSITY IN PATIENTS WITH ORG**

We recently demonstrated that the individual value of glomerular density (non-sclerotic glomerular number per renal cortical area of a needle biopsy) exhibits an ~7-fold variation in IgA nephropathy patients with an estimated glomerular filtration rate of 60 ml/min/1.73 m² or more at the time of a renal biopsy [28]. Of note, the glomerular density was shown to be inversely correlated with the mean glomerular volume, and a low glomerular density is a plausible independent predictor of progression in such patients. This relationship between the glomerular density and the progression of renal disease has also been demonstrated in patients with idiopathic membranous nephropathy [29]. Furthermore, low glomerular density is associated with a blunted response to corticosteroid therapy in patients with minimal change nephrotic syndrome [30]. Based on these findings, we consider that a low glomerular density at the time of a preserved renal function is a plausible predictor of worse renal outcomes and that the glomerular density observed on a renal biopsy can, at least in part, reflect the personal number of nephrons in an individual.

More recently, we found the glomerular density to be extremely low in ORG patients [31]. Such an uneven distribution of the glomerular density in patients with ORG is in sharp contrast to the widely-distributed glomerular density observed on biopsies of kidney transplant donors and patients with IgA nephropathy. In addition, an analysis of the glomerular density in autopsy kidneys without renal disease suggested that such a low level of glomerular density is observed only in ORG patients and is rarely seen in overweight or obese individuals in the absence of chronic kidney disease (CKD). Despite marked glomerulomegaly in ORG patients, there was only a modest increase in the glomerular volume in overweight or obese autopsy kidneys without renal disease. These results suggest that a low glomerular density associated with glomerulomegaly is a characteristic renal histological finding in patients with ORG and that such a difference in glomerular density is not simply related to BMI.

Although the low glomerular density observed in the renal biopsies of ORG patients may be represented by several factors including hypertrophy of the kidneys, the results of our study suggest that the number of nephrons in ORG patients is lower
than that observed in patients with other renal diseases or individuals without renal disease, even in the absence of any apparent renal dysfunction. However, it is uncertain whether the glomerular density observed on a renal biopsy specimen really represents the total number of nephrons in the entire kidney since data on the total cortical volume of the kidney were not available in our study. Accurately determining the origin of the low glomerular density found in ORG patients therefore requires further investigation, including validation of the technique.

NEPHRON MASS–BODY SIZE MISMATCH

A recent study using autopsies without any apparent renal disease demonstrated that several factors, including a high BMI and a low total glomerular number, are associated with increased glomerular volume [32]. Likewise, in an analysis of a patient cohort that included various origins of renal injury, we recently demonstrated that a high BMI and a low glomerular density on a biopsy are factors that are independently associated with an increased mean glomerular volume [33]. Of note, the analyses using the glomerular density/BMI ratio showed a closer association with the mean glomerular volume than the analyses using each measure separately. These results support the mismatch hypothesis, in which the synergism between increased body size and nephron mass reduction is involved in the development of glomerular enlargement and subsequent adaptation failure. As in ORG patients, an increased body size caused by extreme muscle development is associated with similar histopathological findings in ORG patients, i.e. glomerulomegaly and FSGS, thus suggesting that body size is primarily important in this type of renal injury [34]. However, it is also likely that most body builders do not exhibit urinary abnormalities or renal dysfunction, again suggesting that body size alone is not a factor responsible for renal injury. Therefore, the pathogenesis of ORG may include a mismatch between a reduced nephron mass and an increased body size. Glomerular enlargement and scarring caused by such a mismatch may result in a further reduction of the nephron mass, thus leading to a vicious cycle of glomerular compensatory failure and injury.

ORIGINS OF NEPHRON MASS REDUCTION

As described above, clinical and experimental evidence suggests that an absolute reduction in the number of nephrons may sensitize renal injury in obese patients. The origins of reductions in the number of nephrons in people without any apparent renal morphological or functional abnormalities, such as congenital renal agenesis or aplasia, are still incompletely understood. Recent autopsy studies have demonstrated much larger variability in the number of nephrons in normal populations than previously suspected [35, 36]. Therefore, glomerular hyperfiltration may be much greater in individuals who are born with a substantially reduced number of nephrons who then develop obesity. It is known that the number of human nephrons is determined in the last stage of gestation (34–36 weeks) and it does not increase after birth [37]. It is therefore postulated that the fetal environment strongly influences the number of nephrons in an individual. In addition, the number of nephrons is correlated with birth weight [35], and a low birth weight has been postulated to be a risk factor for hypertension, cardiovascular disease and a progression of renal disease in later life [38, 39]. Experimentally, rats grown on a low calorie diet during the gestation period develop obesity, metabolic syndrome, diabetes and hypertension when fed a high calorie diet after birth [40]. The body size–nephron mass mismatch potentially involved in ORG may therefore include such backgrounds that originate from the fetal environment. Therefore, an analysis of birth weight in obese subjects with ORG would be of interest. In a wide sense, other potential origins of nephron number reduction that may be related to renal injury in obese patients include nephron mass reduction due to congenital renal agenesis or aplasia (described above), nephrectomy and CKD of any cause (described below) that develop later in life. Furthermore, it is known that normal aging is associated with a decreased number of nephrons, thus suggesting that aging is a risk factor for obesity-induced renal injury [36]. The congenital and acquired origins of nephron mass reduction that may sensitize renal injury in obese patients are listed in Table 1.

IMPLICATIONS FOR CKD

Clinically, a reduction in nephron mass is most frequently observed during the progression of CKD. In progressive CKD, the rate of sclerotic glomeruli increases in accordance with the progression of renal impairment, and the remnant glomeruli exhibit compensatory enlargement. In processes such as a nephron mass reduction in CKD patients, obesity may additionally affect renal impairment. For example, Bonet et al. [41] reported a BMI of 25 kg/m² or more to be a risk factor for disease progression in patients with IgA nephropathy. Morales et al. [42] found that weight loss is effective for attenuating the progressive loss of the renal function in obese patients with diabetic or non-diabetic renal disease. These results suggest that obesity additively contributes to the further progression of already recognized CKD.

Table 1. Origins of nephron mass reduction that may sensitize renal injury in obese patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td>A low number of nephrons associated with a low birth weight or preterm birth</td>
</tr>
<tr>
<td></td>
<td>Renal agenesis or aplasia</td>
</tr>
<tr>
<td>Acquired</td>
<td>Renal agenesis or aplasia</td>
</tr>
<tr>
<td></td>
<td>Chronic kidney disease (all causes)</td>
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<tr>
<td></td>
<td>Aging</td>
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Recent epidemiological studies have demonstrated obesity to be a risk factor for the appearance of new-onset CKD in community-based populations [43, 44]. As described above, the human nephron number varies, which is, at least in part, explained by different fetal environments between individuals. Consequently, a difference in the renal functional reserve at the time of a normal renal function, i.e. the number of nephrons in individuals, may be a cause of different renal outcomes in patients with chronic renal diseases. The hypothesis of fetal programming of adult diseases is fully consistent with the concept of CKD that involves the coexistence of renal disease, cardiovascular disease and related risk factors, including obesity [38]. Therefore, nephron mass reduction can exist not only in individuals with established CKD, but also in individuals who have not yet developed CKD. Obesity may increase the risk of CKD in individuals with a low number of nephrons, even in the absence of any apparent renal impairment.

**CONCLUSION**

Clinical and experimental evidence suggest that ORG not only reflects obesity-induced renal injury, but also often accompanies a state of renal mass reduction. Both of these factors appear to synergistically contribute to the development of ORG.

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**CONFLICT OF INTEREST STATEMENT**

None declared.

**REFERENCES**


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