Low Glomerular Density with Glomerulomegaly in Obesity-Related Glomerulopathy

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Summary

Background and objectives Obesity-related glomerulopathy is a secondary form of glomerular disease that may occur in obese individuals. It is histologically characterized by marked glomerulomegaly closely related to glomerular hyperfiltration. This study examined glomerular density (nonsclerotic glomerular number per renal cortical area of biopsy specimen) in patients with obesity-related glomerulopathy to determine whether any differences in this measure is associated with disease status.

Design, setting, participants, & measurements Glomerular density and glomerular volume in renal biopsy samples from patients with obesity-related glomerulopathy were compared with those of kidney transplant donors and patients with IgA nephropathy. Kidneys obtained from persons without renal diseases during autopsy were also analyzed to investigate the effects of obesity on glomerular density and glomerular volume.

Results Glomerular density of kidneys from patients with obesity-related glomerulopathy ($1.7 \pm 0.6/mm^2$) was significantly lower than that in biopsy samples from kidney transplant donors ($3.1 \pm 1.0/mm^2$) and patients with IgA nephropathy ($3.5 \pm 1.5/mm^2$). However, an analysis of autopsy cases without renal diseases showed that the glomerular density in overweight ($2.9 \pm 0.7/mm^2$) or obese ($3.1 \pm 1.1/mm^2$) persons was similar to that in non-obese ($3.1 \pm 0.6/mm^2$) individuals. Biopsy specimens of patients with obesity-related glomerulopathy showed marked glomerulomegaly. However, glomerular volume was only modestly increased in the autopsy-examined kidneys from overweight or obese persons without renal diseases.

Conclusions Low glomerular density associated with glomerulomegaly may be a characteristic histologic finding of patients with obesity-related glomerulopathy.

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Introduction

The presence of proteinuria as a complication of massive obesity was first reported in 1974 (1). Several cases have subsequently been reported (2–5), and this renal complication is recognized as obesity-related glomerulopathy (ORG) (6–8). In general, however, the absolute risk that an obese individual will develop progressive renal deterioration is very low. Therefore, obesity seems not to be sufficient to cause such severe renal injuries, and other factors probably contribute to the development of ORG.

Studies have suggested a relationship between obesity and increased GFR (9,10). Glomerular hyperfiltration in obese persons has been postulated to lead to structural abnormalities in glomeruli, such as glomerulomegaly and FSGS, in a manner analogous to that described in reduced renal mass states (11,12). Therefore, a difference in nephron number may be related to the pathogenesis of renal injury in ORG (13,14). Indeed, recent autopsy studies have demonstrated a much larger variability in nephron number in normal populations than had been suspected (15,16).

We recently demonstrated that the individual value of glomerular density (GD; nonsclerotic glomerular number per renal cortical area of biopsy specimen) varies approximately seven-fold in patients with IgA nephropathy (IgAN) who maintain renal function (17). Notably, GD is inversely correlated with glomerular volume (GV), and low GD is a plausible independent predictor of progression in those patients. These findings led to the hypothesis that the GD on renal biopsy specimens can, at least in part, reflect the personal nephron number of each individual. This study examined GD in patients with ORG to determine whether any differences in such a histologic measure is associated with disease status.

Materials and Methods

Patient Selection

This study included patients who underwent renal biopsy at Jikei Hospital, Tokyo, Japan, from 1999 to 2008. The indications for biopsy were persistent proteinuria of >0.5 g/d or progressive loss of renal function. Obesity was defined as a body mass index (BMI)

≥30 kg/m^2. ORG was morphologically defined as obesity-associated glomerulomegaly with or without FSGS lesions, as reported previously (7). Renal biopsy samples showing any clinical and histologic evidence of other primary or secondary renal diseases, including diabetic nephropathy, were carefully eliminated. The appearance of an increased glomerular basement membrane thickness alone was not a criterion for exclusion because studies have suggested that obese patients or those with ORG can have an increased glomerular basement membrane thickness in the absence of diabetes (18,19). Hypertension was not an exclusion criterion. In our initial exclusion process, we found that biopsy specimens from some obese hypertensive patients showed moderate to severe vascular lesions, which were accompanied by the collapsing of glomeruli. In patients with such histologic features, hypertensive nephrosclerosis was diagnosed instead of ORG; these patients were excluded from this study. Any patients with moderately impaired renal function at biopsy, which was defined as estimated GFR (eGFR) <60 ml/min per 1.73 m^2, were excluded to minimize the effects of any renal compensatory changes due to advanced chronic injury. Patients whose renal tissue specimens contained fewer than 10 glomeruli (including globally sclerotic glomeruli) were also excluded.

Thirty patients with a diagnosis of ORG were recruited from the renal biopsy archives during this period. Nine of these 30 patients showed moderately impaired renal function on diagnosis (eGFR < 60 ml/min per 1.73 m^2) and thus were excluded. One of the remaining 21 renal biopsy samples contained fewer than 10 glomeruli and thus was excluded. Thus, 20 biopsy samples from 20 patients with ORG were included in this study.

Renal biopsy specimens from kidney transplant donors and patients with IgAN (17) were also analyzed for comparison. Kidney transplant donors were used to represent persons without apparent CKD, and patients with IgAN, the most common form of primary glomerular disease, represented those with chronic renal injury. The inclusion criteria for these patient cohorts were an eGFR ≥60 ml/min per 1.73 m^2 at biopsy and more than 10 glomeruli (including globally sclerotic glomeruli) in biopsy specimens.

Autopsy Cases

We analyzed kidneys obtained from autopsies performed at Jikei Hospital. Potential cases were identified by a retrospective analysis of the autopsy database from 2006 to 2010. The included cases were required to have had a full autopsy. Any cases with evidence suggesting a history of CKD, including those with impaired renal function (eGFR < 60 ml/min per 1.73 m^2) or persistent urinary abnormalities, were excluded. Cases were also excluded if the kidney tissue contained any histologic abnormalities suggesting chronic renal diseases or malignancies.

Definitions

The eGFR was calculated by applying a modified three-variable equation for estimating the GFR for Japanese persons (20):

$$eGFR = 194 \times Age^{-0.287} \times sCr^{-1.094} \ (\times 0.739 \ if \ female),$$

where sCr is serum creatinine. The BP was measured at least twice with patients in the seated position. Hypertension was defined as systolic BP over 140 mmHg or diastolic

Table 1. Clinical and histopathologic characteristics at biopsy

Characteristics	Kidney Donors (n=20)	Patients with IgAN (n=98)	Patients with ORG (n=20)	P Value	
				Donor versus ORG	IgAN versus ORG
Clinical					
age (yr)	59±9	34±13	40±12	<0.001	0.04
men (%)	35	45	70	0.03	0.05
BMI (kg/m^2)	23.5±3.4	21.8±2.9	32.7±3.3	<0.001	<0.001
estimated GFR (ml/min per 1.73 m^2)	81±18	87±18	80±21	0.71	0.04
patients with hypertension (%)	25	23	65	0.004	<0.001
urinary protein excretion (g/d)	NA	1.1±1.1	1.1±0.7	NA	0.40
Histopathologic					
interstitial fibrosis/tubular atrophy (%)	7±7	18±12	16±11	0.003	0.51
glomeruli affected by global glomerular sclerosis (%)	6±8	13±15	14±13	0.02	0.52
glomeruli affected by segmental glomerular sclerosis (%)	0	6.2±8.2	2.4±4.9	0.28	0.03
patients with segmental glomerular sclerosis (%)	0	51	25	0.04	0.03
GD1 (glomeruli/mm^2)	3.1±1.0	3.5±1.5	1.7±0.6	<0.001	<0.001
GD2 (glomeruli/mm^2)	3.3±1.1	3.9±1.6	1.9±0.7	<0.001	<0.001
GV ($\times 10^6/\mu m^3$)	2.4±0.6	2.9±1.1	6.3±1.8	<0.001	<0.001

Values expressed with a plus/minus sign are the mean ± SD. IgAN, IgA nephropathy; ORG, obesity-related glomerulopathy; BMI, body mass index; GD, glomerular density (GD1: GD excluding global glomerular sclerosis; GD2: GD including global glomerular sclerosis); GV, glomerular volume.

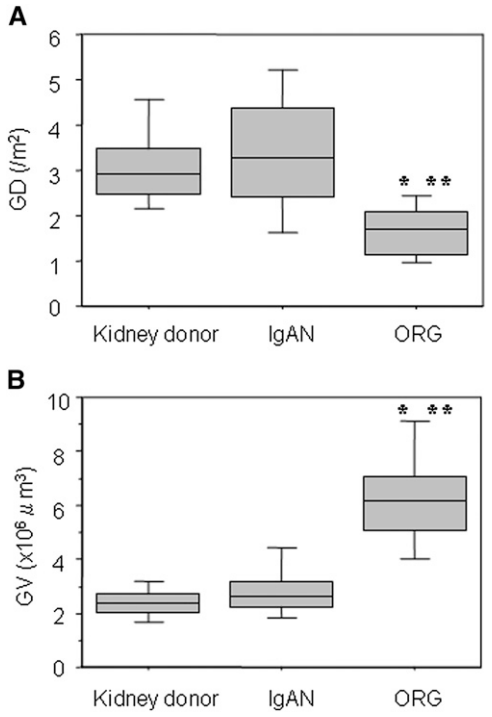

Figure 1. | Comparison of glomerular density (GD) and glomerular volume (GV) in renal biopsy specimens. GD (GD1) (A) and GV (B) in biopsy specimens from patients with obesity-related glomerulopathy (ORG) (n=20) were compared with those from kidney transplant donors (n=20) and patients with IgA nephropathy (IgAN) (n=98). *P<0.05 versus kidney donors; **P<0.05 versus patients with IgAN. The lines of each box plot and the error bars represent mean ± SD.

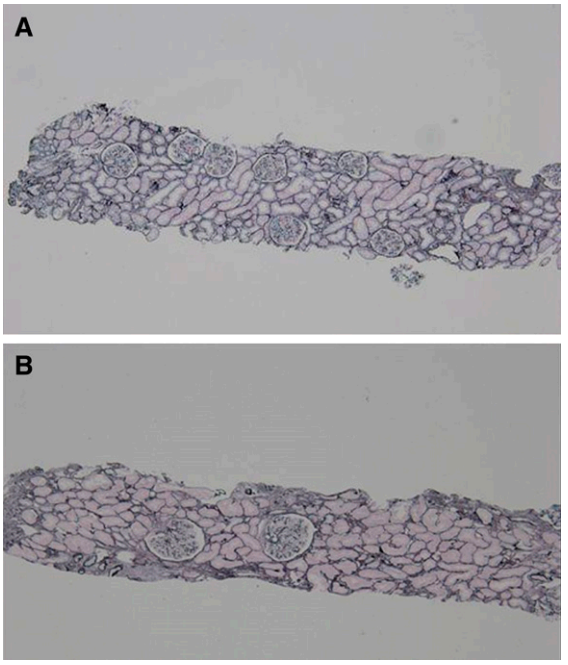

Figure 2. | Representative renal biopsy findings on light microscopy. (A) Kidney transplant donor (36-year-old normotensive woman with estimated GFR of 109 ml/min per 1.73 m^2 and body mass index of 24.8 kg/m^2). (B) Patient with obesity-related glomerulopathy (23-year-old normotensive man with estimated GFR of 79 ml/min per 1.73 m^2 and body mass index of 32.5 kg/m^2). Periodic acid-methenamine silver stain; original magnification, ×50.

BP over 90 mmHg or use of antihypertensive medications. The patients using antihypertensive medications, such as angiotensin blockers, for renoprotection despite normal BP were considered normotensive.

Pathologic Analysis

All the renal biopsy specimens of patients with IgAN and those with ORG were obtained by performing a percutaneous needle biopsy. The renal biopsies of kidney transplant donors were performed using a needle biopsy gun under direct vision. The renal biopsy specimens at 1 hour after renal transplantation were used for the analyses. An 18-gauge biopsy needle was used for all biopsy cases in this study. The tissues were embedded in paraffin, cut into 3- to 4-μm sections, and stained with hematoxylin-eosin, periodic acid-Schiff, Masson trichrome, and periodic acid-methenamine silver stain. All biopsy specimens investigated in this study were subjected to immunohistochemical and electron microscopic analyses for evaluation. The percentage of glomeruli affected by segmental or global sclerosis was assessed. The area of interstitial fibrosis or tubular atrophy was semiquantitatively evaluated according to the percentage of cortical area involvement.

The GD was determined by calculating the number of glomeruli per total renal cortical area and was measured using a computed imaging analyzer (Leica IM500, Leica Microsystems, Germany). The measurement of GD is strongly influenced by the degree of global sclerosis. Therefore, two different definitions of GD were applied: the number of glomeruli that were not globally sclerotic per total renal cortical area (GD1) and the number of all glomeruli (including globally sclerotic glomeruli) per total renal cortical area (GD2). The glomerular area was defined as the area described by the outer capillary loops of the tuft using a computed imaging analyzer (Leica IM500). The mean glomerular area (GA) was calculated by averaging the areas of all the glomeruli. The mean GV was calculated from the measured GA:

$$GV = (GA)^{3/2} X\beta/d,$$

where β is a dimensionless shape coefficient (β = 1.38 for spheres) and d is a size distribution coefficient used to adjust for variations in glomerular size (21). The analysis used d = 1.01, as in previous studies (22,23). The number of glomeruli was counted at four randomly selected fields in the outer to mid cortex with a magnification of ×50 (6 mm^2 each) to determine the GD in autopsy cases. About 50 glomeruli were randomly selected in autopsy cases, and the GV was calculated from the measured GA as described above.

Statistical Analyses

Continuous variables are expressed as the mean ± SD. The variables were assessed for normality both visually (normal probability plot) and by inferential statistics (Shapiro-Wilk W and Kolmogorov-Smirnov tests). Continuous variables were compared by the t test or the Wilcoxon

Table 2. Clinical and histopathologic findings in autopsy cases categorized by body mass index

Characteristics	Nonobese (n=25)	Overweight (n=15)	Obese (n=8)	P Value
Clinical				
age (yr)	66±13	60±11	57±13	0.05
men (%)	60	67	75	0.73
BMI (kg/m^2)	19.8±3.0	28.2±1.0	33.9±4.2	<0.001
estimated GFR (ml/min per 1.73 m^2)	88±25	89±30	81±24	0.64
Histopathologic				
left kidney weight (g)	149±30	181±44	213±79	0.01
interstitial fibrosis/tubular atrophy (%)	8±4	6±4	6±2	0.005
glomeruli affected by global glomerular sclerosis (%)	4.5±4.4	1.0±1.5	2.0±2.8	0.008
GD1 (glomeruli/mm^2)	3.1±0.6	2.9±0.7	3.1±1.1	0.40
GD2 (glomeruli/mm^2)	3.2±0.6	2.9±0.7	3.1±1.1	0.30
GV ($\times 10^6/\mu m^3$)	2.4±0.7	3.8±1.5	3.7±1.5	<0.001

Values expressed with a plus/minus sign are the mean ± SD. BMI, body mass index; GD, glomerular density (GD1: GD excluding global glomerular sclerosis; GD2: GD including global glomerular sclerosis); GV, glomerular volume.

rank-sum test to assess significant differences among each group where appropriate. Categorical variables were expressed as a percentage and compared using the chi-squared test. The Kruskal-Wallis test was applied for multiple comparisons of the autopsy cases. A P value < 0.05 was considered to represent a statistically significant difference. All statistical analyses were performed using the SPSS software package (SPSS Inc., Chicago, IL).

Results

Clinical and Histopathologic Characteristics of Patients with ORG

The clinical and histopathologic characteristics of patients with ORG are summarized in Table 1. Characteristics of kidney transplant donors and patients with IgAN are shown for comparison purposes. Patients with ORG were relatively young, and there was a male dominance. Sixty-five percent of patients with ORG had hypertension. The patients with ORG showed mild to moderate levels of chronic renal injuries, including interstitial fibrosis or tubular atrophy, global glomerular sclerosis, and FSGS. In this ORG cohort, eight glomeruli from five patients showed FSGS lesions; most (seven of eight) of these FSGS lesions were perihilar variants, and only a minority (one of eight) was a not-otherwise-specified variant. Typical FSGS lesions showing cellular, collapsing, or tip variants were not identified. The patients with IgAN had almost the same degrees of chronic renal injuries as those found in patients with ORG.

Comparison of GD and GV in Biopsy Cases

The GD of patients with ORG was significantly lower than that in the other patient groups (Figure 1A). The low GD in patients with ORG was still present, even when global glomerular sclerosis was included in the GD calculation (GD2). In contrast, the GV of patients with ORG was much larger than that of the other patient groups (Figure 1B).

Figure 2 shows the representative renal biopsy findings from a kidney transplant donor (Figure 2A) and a patient with ORG (Figure 2B). These patients differed with regard to the density and the size of the glomeruli.

Comparison of GD and GV between Autopsy Kidneys from Patients in Different BMI Categories

Kidneys obtained at autopsy were analyzed to investigate the effects of obesity on GD and GV. The analysis was limited to autopsy cases that showed no evidence of renal diseases and compared several variables among groups categorized according to BMI: nonobese (BMI < 25 kg/m^2), overweight (25 ≤ BMI < 30 kg/m^2), and obese

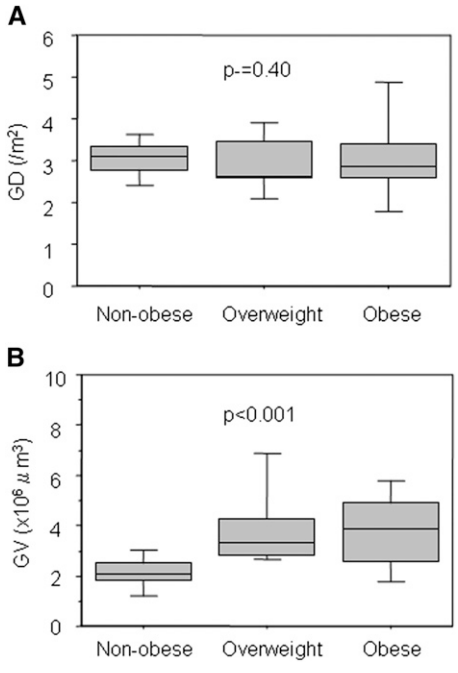

Figure 3. | Comparison of glomerular density (GD) and glomerular volume (GV) in autopsy kidneys. GD (GD1) (A) and GV (B) in the autopsy kidneys without any evidence of CKD were compared among three groups categorized according to body mass index (BMI): nonobese (BMI < 25 kg/m^2, n=25), overweight (25 ≤ BMI < 30 kg/m^2, n=15), and obese (BMI ≥ 30 kg/m^2, n=8). The lines of each box plot and the error bars represent mean ± SD.

(BMI ≥ 30 kg/m^2). Table 2 shows that the degrees of chronic histologic changes, such as interstitial fibrosis or tubular atrophy and global glomerular sclerosis, were very mild in all groups. GD levels did not significantly differ between the groups (Figure 3A). The GV was larger in the overweight group and the obese group than in the nonobese group (Figure 3B). The GD in each of the autopsy kidney groups was similar to that in the kidney transplant donors and the patients with IgAN.

Comparison of GD and GV between Biopsy Specimens from Patients with or without Hypertension

The clinical and histopathologic characteristics of patients with IgAN and those with ORG were compared among groups categorized according to the absence or presence of hypertension (Table 3). Hypertensive patients with IgAN showed a low GD and large GV compared with normotensive patients with IgAN. However, the comparison of GD and GV in normotensive and hypertensive patients with ORG showed no significant differences. In addition, in a separate analysis, the GD of normotensive patients with ORG was significantly lower than that of hypertensive patients with IgAN ($P<0.001$).

Discussion

This study showed GD to be extremely low in patients with ORG. Such an uneven distribution of GD in ORG was in sharp contrast to the widely distributed GD in biopsy specimens from kidney transplant donors and patients with IgAN. In addition, an analysis of GD in autopsy kidneys suggested that such a low GD was observed only in patients with ORG and was rarely seen in overweight or obese individuals without CKD. Despite marked glomerulomegaly in patients with ORG, there was only a modest increase in GV in autopsy kidneys from overweight or obese persons. These results suggest that a low GD associated with glomerulomegaly may be a characteristic renal histologic finding in patients with ORG.

A previous study using autopsy kidneys showed a relationship between essential hypertension and kidneys with few nephrons (24). Hypertension is prevalent in the obese population (14). In fact, 65% of patients with ORG in this study had hypertension at the time of biopsy, and the percentage of patients with hypertension was significantly higher than in other patient groups. Therefore, hypertension may be an obvious candidate associated with the low GD in ORG. However, the comparison of GD in normotensive and hypertensive patients with ORG in this series showed no significant difference. In addition, the GD of normotensive patients with ORG was still significantly lower than that of hypertensive patients with IgAN. Therefore, it is unlikely that hypertension is the only factor associated with the low GD in ORG.

Patients with ORG showed mild to moderate chronic renal injury. Therefore, these histologic factors might affect GD levels. However, the GD in patients with ORG was significantly lower than that in patients with IgAN, who

Table 3. Clinical and histopathologic characteristics of normotensive and hypertensive patients at biopsy

Characteristic	IgAN			ORG		
	Normotensive (n=75)	Hypertensive (n=23)	P Value	Normotensive (n=7)	Hypertensive (n=13)	P Value
Clinical						
age (yr)	31±11	42±15	0.003	34±12	43±11	0.07
men (%)	39	70	0.009	57	77	0.49
BMI (kg/m^2)	21.2±2.5	23.7±3.3	0.001	32.6±3.3	32.7±3.4	0.70
estimated GFR (ml/min per 1.73 m^2)	90±18	76±12	0.001	88±24	76±18	0.07
urinary protein excretion (g/d)	1.0±1.1	1.2±1.0	0.20	1.1±1.0	1.1±0.5	0.45
Histopathologic						
interstitial fibrosis/ tubular atrophy (%)	16±11	24±15	0.006	15±13	16±10	0.64
glomeruli affected by global glomerular sclerosis (%)	12±14	17±17	0.15	11±16	15±11	0.24
glomeruli affected by segmental glomerular sclerosis (%)	5.7±7.0	7.5±11.3	0.88	1.1±2.0	3.0±5.9	1.00
patients with segmental glomerular sclerosis (%)	51	52	0.90	29	23	0.88
GD1 (glomeruli/mm^2)	3.8±1.5	2.5±1.0	<0.001	1.6±0.8	1.7±0.5	0.70
GD2 (glomeruli /mm^2)	4.2±1.6	2.9±1.0	0.001	1.8±0.8	2.0±0.6	0.44
GV ($\times 10^6/\mu m^3$)	2.6±1.0	3.8±1.0	<0.001	6.1±2.2	6.4±1.7	0.64

Values expressed with a plus/minus sign are the mean ± SD. IgAN, IgA nephropathy; ORG, obesity-related glomerulopathy; BMI, body mass index; GD, glomerular density (GD1: GD excluding global glomerular sclerosis; GD2: GD including global glomerular sclerosis); GV, glomerular volume.

had almost the same degrees of chronic renal injuries as those found with ORG. In addition, there was still a significant difference between GD in the ORG group and GD in other patients groups, even when global glomerular sclerosis was included in the calculation of GD. Therefore, it is not likely that the different GD levels are simply due to chronic renal injuries. However, the globally sclerotic glomeruli may have merged and disappeared over the long term and modified GD. In addition, the low GD may represent hypertrophy of the kidneys. The presence of tubular hypertrophy may result in low GD because most renal tissues are composed of renal tubules. The weight of the autopsy kidneys tended to increase in parallel with BMI, a finding consistent with that of a previous study (15). However, GD did not significantly differ between the groups categorized by BMI. The finding of a larger kidney weight with a similar GD may imply that the glomerular number is higher in the obese autopsy cases than in the nonobese autopsy cases. It has been clearly shown that the total nephron number is inversely correlated with age (15). We therefore concluded that this result may, at least in part, be related to the fact that the obese patients examined at autopsy were younger than the nonobese patients.

Recent autopsy studies have demonstrated a much larger variability in nephron number in normal populations than had been suspected (15,16). In addition, the number of nephrons is correlated with birth weight (16), and low birth weight is postulated to be a risk factor for hypertension, cardiovascular diseases, and progression of renal diseases in later life (25–27). Therefore, glomerular hyperfiltration may be much greater in individuals who are born with a substantially reduced number of nephrons and who then develop obesity. Alternatively, such a mismatch would also be possible in situations of acquired reduction in nephron number, such as uninephrectomy in obese persons (28) or the coexistence of CKD and obesity (29,30). These findings, together with the current results, support the possibility that a mismatch between reduced nephron number and obesity-induced increased metabolic demands leads to the development of renal injury (13,14,31).

This study has several limitations. It is uncertain whether the GD on a renal biopsy specimen represents the total nephron number of the whole kidney because data on birth weight in patients with ORG or the total cortical volume of the kidney were not available. Therefore, the finding of a low GD does not prove that patients with ORG have a low number of glomeruli. Accurately determining the origin of the low GD in patients with ORG therefore requires further investigations.

In conclusion, this study shows that GD in patients with ORG is extremely low. An analysis of autopsy kidneys from persons without renal diseases indicated that such a difference in GD is not simply related to BMI. These results suggest that a low GD, in addition to marked glomerulomegaly, may be a characteristic histologic finding of patients with ORG.

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Disclosures

None.

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