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Glomerular enlargement correlated with body mass index is a distinct characteristic of obesity-related glomerulopathy

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Background: Obese people without diabetes mellitus have proteinuria and kidney dysfunction termed obesity-related glomerulopathy (ORG).
Objective: We retrospectively investigated the clinical and histological characteristics of ORG.
Methods: Patients who underwent a kidney biopsy from 2001 to 2010 were screened for this study. Patients with primary glomerular diseases with immunoglobulin and complement deposition, secondary and congenital kidney diseases, or steroid-responsive minimal change nephrotic syndrome were excluded. Patients were divided into non-obese (<23 kg/m^2), intermittent obese (23 to <25), and obese (≥25) groups according to body mass index (BMI), and the clinical and histological indices were examined.
Results: Thirty-six non-obese, 8 intermediate obese, and 16 obese patients were identified from the 995 kidney biopsy-proven patients. The clinical indices, except gender, were not significantly different among the three groups. Histologically, the glomerular diameter was significantly larger in the obese group than in the non-obese group. BMI was significantly correlated with glomerular diameter (γ = 0.487, P < 0.0001, n = 60). Focal segmental glomerular sclerosis (FSGS) lesions were found in 62% of the obese patients, and 60% of those FSGS lesions were tip variants.
Conclusions: The most distinct characteristic of ORG was glomerular enlargement. The tip variant of FSGS is a possible lesion of ORG.

Key words: obesity-related glomerulopathy, obesity, BMI (body mass index)

Introduction

Much attention has been paid to proteinuria and renal dysfunction in obese people without diabetes mellitus (DM) as obesity-related glomerulopathy (ORG). The Adults Treatment Panel III (ATP) of the National Cholesterol Education Program, based on data in the United States,[1] defined obesity as a body mass index (BMI) of ≥30 kg/m^2; however, the Japan Society for the Study of Obesity reported that obesity is adequately specified as a BMI of ≥25 kg/m^2 in Japan for Asians.[2] And a modified version of ATPIII-BMI 25, which defined obesity as a BMI of ≥25, in the Japanese population was comparable to the original ATPIII in a white population for the determination of metabolic syndrome.[3] Japanese people with a BMI of 23.0-24.9 also had higher risks for obesity-associated disorders.[4]

The histological characteristics of ORG include glomerular swelling, mesangial matrix expansion, glomerular basement membrane (GBM) thickening, and focal segmental glomerular sclerosis (FSGS).[5-7] Although Kambham et al.[8] reported that ORG was associated with lower levels of proteinuria than ORG with FSGS and that the incidence rates of nephritic syndrome were 5.6% in ORG and 54% in primary FSGS, some of the clinical and histological profiles and the prognosis of ORG remain unknown. Therefore, in this study, we retrospectively investigated the clinical and histological characteristics of ORG in Japanese patients.

Materials and Methods

Patients

All patients who underwent a renal biopsy in the

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Department of Nephrology of Kitasato University Hospital from 2001 to 2010 and who were aged >20 years were enrolled in this study. According to the pathological and clinical diagnoses, we excluded patients with primary glomerular diseases of membranous nephropathy, membranoproliferative glomerulonephritis, acute glomerulonephritis, IgA glomerulonephritis, or idiopathic crescentic glomerulonephritis, and those with secondary renal diseases of lupus nephritis, microscopic polyangiitis, Wegener granulomatosis, Goodpasture's syndrome, anti-GBM antibody nephritis, purpura nephritis, antiphospholipid antibody syndrome, hemolytic-uremic syndrome, hepatitis B virus-associated nephritis, hepatitis C virus-associated nephritis, cryoglobulinemic vasculitis, MRSA (methicillin-resistant staphylococcus aureus)-associated nephritis, infectious glomerulonephritis, DM, myeloma kidney, renal amyloidosis, microfibrillar disease, light and heavy chain deposition disease, cholesterol embolism, immunoglobulin (Ig)G4-related syndrome, malignant nephrosclerosis, drug-induced tubulointerstitial nephritis, Sjögren's syndrome, Castleman's syndrome, POEMS (polyneuropathy, organomegaly, endocrinopathy or edma, M-protein, skin abnormalities) syndrome, and HIV (human immunodeficiency virus)-associated nephropathy. Patients with the congenital renal diseases of Alport syndrome and thin basement membrane disease were also excluded. Patients with a history of DM, hemoglobin A1c (HbA1c) >6.2% or a diabetic pattern following a 50-g oral glucose tolerance test performed at the time of renal biopsy were also excluded as patients with DM. Patients with steroid-responsive nephrotic syndrome with proteinuria of <0.3 g/day after 4 weeks of treatment with 0.4 mg/kg/day oral prednisolone were excluded as steroid-responsive minimal change nephrotic syndrome (MCNS). The remaining patients with pauci-immune-type glomerulopathy were divided into non-obese (<23 kg/m^2), intermittent obese (23 to <25 kg/m^2), and obese (≥25 kg/m^2) groups. Patients with asymptomatic microscopic hematuria and no abnormal findings in their kidney specimens were included as a control group.

Methods

We retrospectively investigated and compared the clinical and histological characteristics of the three groups at the renal biopsy. Age, gender, duration of proteinuria, history of smoking, body height, body weight (BW) without edema, BMI, blood pressure, proteinuria, hematuria, serum albumin, serum urea nitrogen, serum creatinine, estimated glomerular filtration ratio (eGFR), HbA1c, serum total cholesterol, serum low density lipoprotein (LDL)-cholesterol, and serum high density lipoprotein (HDL)-cholesterol were recorded. BW without edema was defined as the BW before or at remission of acute diseases or within 3 months before and after the renal biopsy.

Light microscopic examination of kidney biopsy specimens was performed after staining the tissue samples with hematoxylin-eosin, periodic acid-Schiff, or Masson trichrome. Immunofluorescence for IgG, IgA, IgM, C1q, C3, C4, and fibrinogen was evaluated. Electron microscopic specimens were also evaluated. Patients with complete data for light and electron microscopy and immunofluorescence, and light microscopic specimens with >20 glomeruli in their kidney biopsy specimens were included in this study. Using biopsy specimens, 2 nephrologists independently determined the glomerular diameter, the ratio of global sclerosis in glomeruli, the ratio of FSGS lesions in glomeruli, the classification of FSGS lesions according to the Columbia classification,[9] the ratio of tubular atrophy, the area of mononuclear cell infiltration, and the presence of arteriolosclerosis.

To calculate the maximum glomerular diameter, 8 consecutive kidney biopsy specimens (3-μm thick) were observed, and the maximum glomerular diameter within the 8 consecutive specimens was measured. The mean diameter of 6-10 glomeruli of a patient was defined as the mean glomerular diameter for that patient. The diameter of control glomeruli was measured by the same method using kidney specimens from patients with asymptomatic microhematuria and negative findings of light microscopy, electron microscopy, and immunofluorescence. We defined diffuse lesions as any lesion in >50% of the glomeruli. Global or segmental glomerular lesions were defined as lesions in more or less than 50% of the glomerular tufts, respectively. FSGS lesions were classified as FSGS not otherwise specific (NOS), perihilar variant, cellular variant, tip variant, and collapsing variant, according to the Columbia classification.[9] Tubular atrophy and interstitial fibrosis were semiquantitatively evaluated according to the four-grade system[10] as follows: grade 0, no lesions (0%); grade 1, lesions covering 1%-25% of the cortical area; grade 2, lesions covering 26%-50% of the cortical area; and grade 3, lesions covering ≥51% of the cortical area. Arteriolosclerosis was evaluated using the most advanced part of arteriolosclerosis based on the formula: width of the intima/width of the intima and media.[10] All studies were performed with the approval of the Clinical Studies and Ethics Committee of Kitasato University Hospital.

Statistical analyses

Data were analyzed using JMP® version 9.0 (SAS Institute Inc., Cary, NC, USA). Paired and unpaired Student's *t* tests and the Tukey-Kramer test were applied for normally distributed variables. The Wilcoxon rank sum test and the Kruskal-Wallis test were used for non-normally distributed variables. Fisher's exact test was also used as appropriate. Data are expressed as the mean ± SD. Differences with P-values of <0.05 were considered to be statistically significant.

Results

Patient selection

A total of 995 patients who underwent a kidney biopsy at Kitasato University Hospital from January 2001 to December 2010 were enrolled in this study (Figure 1). Of these, 816 patients with 1 of 33 primary, secondary, or congenital kidney diseases were excluded, as were 100 patients with steroid-responsive MCNS. The pathological diagnoses of the remaining 79 patients were pauci-immune type glomerulopathy of minor glomerular abnormalities, non-IgA mesangial proliferative glomerulonephritis (GN), FSGS, benign nephrosclerosis, or unclassified kidney disease. Of the 79 patients, 45 patients were classified as non-obese, 11 as intermediate obese, and 23 as obese based on their BMI. For 9, 3, and 7 patients in the non-obese, intermediate obese, and obese groups, respectively, the kidney biopsy specimen was inadequate to measure glomerular diameter. Therefore, a total of 60 patients, with 36, 8, and 16 patients in the non-obese, intermediate obese, and obese groups, respectively, were included in the present study.

Patient clinical characteristics

There were significantly more males in the obese group

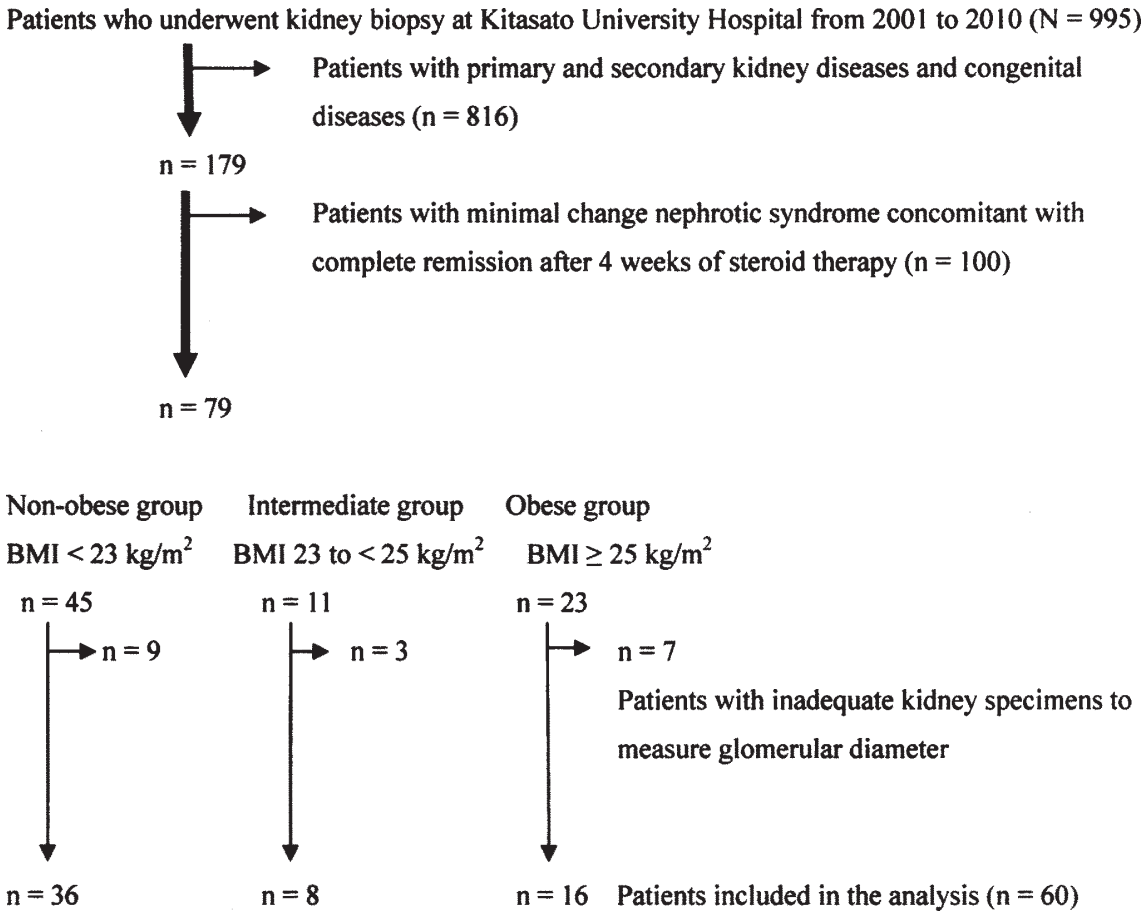

Figure 1. Patient disposition

A total of 79 of 995 patients without primary, secondary or congenital kidney diseases who underwent kidney biopsy at Kitasato University Hospital from 2001 to 2010 were included in this study. The patients had unknown kidney diseases without immunoglobulin or complement deposition on the glomeruli. The patients with pauci-immune type glomerular diseases were divided into non-obese (<23 kg/m^2; n = 36), intermediate obese (23 to <25 kg/m^2; n = 8), and obese (≥25 kg/m^2; n = 16) groups.

than in the non-obese group (Table 1). BW and BMI were greatest in the obese group followed by those in the intermediate obese group. There were no significant differences in age, body height, duration of proteinuria, duration of smoking, or systolic/diastolic blood pressure among the three groups (Table 1). Urinary protein and urinary occult blood were not significantly different among the three groups (Table 2), nor were the serum levels of albumin, urea nitrogen, creatinine, eGFR, HbA1c, total cholesterol, LDL-cholesterol, and HDL-cholesterol significantly different (Table 2).

Histological features of renal biopsy specimens

Although FSGS was apparent in 63%, 38%, and 42% of patients in the obese, the intermediate obese, and in the non-obese groups, respectively, these differences were not statistically significant (Table 3). The variants of FSGS defined according to the Colombia classification in the non-obese group (n = 15) included NOS in 5 patients (33%), perihilar in 2 (13%), cellular in 1 (7%), and tip variants in 7 patients (47%). Among patients in the obese group (n = 10), the variants were NOS in 1 (10%), perihilar in 1 (10%), cellular in 2 (20%), and tip variants in 6 patients (60%). In the intermediate obese group (n = 3) 1 patient each had NOS, perihilar, and tip variants. The

Table 1. Patient characteristics at kidney biopsy

Characteristic BMI (kg/m^2)	Non-obese group <23	Intermediate obese group 23 to <25	Obese group ≥25
n	36	8	16
Age	44 ± 18	55 ± 21	50 ± 16
Gender (M/F)	19/17	6/2	14/2[a]
Body height (cm)	162 ± 9	161 ± 10	169 ± 8
Body weight (kg)	52 ± 8	63 ± 9[b]	75 ± 11[cd]
BMI (kg/m^2)	19.8 ± 1.7	24.2 ± 0.6[d]	26.8 ± 1.6[de]
Duration of proteinuria (mo)	73 ± 75	59 ± 52	93 ± 95
Duration of smoking (mo)	113 ± 165	230 ± 224	129 ± 185
Systolic BP (mmHg)	129 ± 22	134 ± 13	138 ± 20
Diastolic BP (mmHg)	78 ± 14	84 ± 12	84 ± 13

Values are means ± SD.
The Kruskal-Wallis test was employed for this analysis.
[a]P = 0.03 vs. the non-obese group; [b]P < 0.02 vs. the non-obese group; [c]P < 0.01 vs. the intermediate obese group; [d]P < 0.001 vs. the non-obese group; [e]P = 0.001 vs. the intermediate group

Table 2. Blood chemistry at kidney biopsy

BMI (kg/m^2)	Non-obese group <23	Intermediate obese group 23 to <25	Obese group ≥25
n	36	8	16
Urinary protein (g/d)	3.2 ± 3.3 (36)	3.6 ± 4.2 (8)	5.1 ± 4.8 (16)
Urinary occult blood	1.5 ± 1.4 (36)	1.0 ± 1.2 (8)	1.9 ± 1.3 (16)
Serum albumin (g/dl)	3.3 ± 1.1 (36)	3.1 ± 1.2 (8)	3.2 ± 1.1 (16)
Serum urea nitrogen (mg/dl)	17.7 ± 10.4 (36)	30.6 ± 19.4 (8)	18.6 ± 11.9 (16)
Serum creatinine (mg/dl)	1.1 ± 0.9 (36)	1.3 ± 0.6 (8)	1.3 ± 0.7 (16)
eGFR (ml/min)	72.4 ± 28.8 (36)	50.7 ± 21.8 (8)	58.6 ± 24.6 (16)
HbA1c (%)	5.5 ± 0.4 (13)	5.2 ± 0.6 (4)	5.6 ± 0.3 (10)
Serum total cholesterol (mg/dl)	311 ± 151 (36)	326 ± 100 (8)	311 ± 149 (16)
Serum LDL cholesterol (mg/dl)	218 ± 135 (28)	208.6 ± 81 (7)	231.9 ± 144 (14)
Serum HDL cholesterol (mg/dl)	76.1 ± 32 (22)	62 ± 22 (4)	56 ± 28 (13)

Values are means ± SD.
The Kruskal-Wallis test was employed for this analysis.
Urinary occult blood was scored as: - (0), ± (1), 1+ (2), 2+ (3), or 3+ (4).

collapsing variant was not detected in any patients in any of the groups. There were no significant differences in the frequencies of each variant of FSGS between the non-obese and obese groups. Similarly, the frequencies of minor glomerular abnormalities, non-IgA mesangial proliferative lesions, arteriolosclerosis, and unclassified lesions were not significantly different among the three groups (Table 3).

The mean glomerular diameters in the obese (207 ± 20 μm) and intermediate obese (191 ± 21 μm) groups were significantly higher than that in the control group (160 ± 13 μm, Table 4, Figure 2). The mean glomerular diameter increased from the non-obese group to the obese group and was significantly correlated with BMI (y = 11.75 ± 0.34 × BMI; r = 0.487, P < 0.0001, n = 60) in the total cohort of patients (Figure 3). The percentage of glomerular sclerosis, percentage of FSGS lesion, mesangial cell proliferation, tubular atrophy, interstitial cell infiltration, interstitial fibrosis, and arteriolar intima thickness were not significantly different among the three groups (Table 4).

Clinical course of kidney function

The eGFR at kidney biopsy was 72 ± 29 ml/min in the non-obese group and 58 ± 25 ml/min in the obese group, which was not significantly different. The eGFRs at 5 and 8 years after kidney biopsy were 67 ± 26 ml/min (P = 0.025 vs. at kidney biopsy) and 72 ± 21 ml/min (P = 0.011 vs. at kidney biopsy), respectively, in the non-obese group. The respective eGFRs in the obese group were 52 ± 21 ml/min (P = 0.056 vs. at kidney biopsy) and 49 ± 18 ml/min (P = 0.437 vs. at kidney biopsy) (Figure 4).

Table 3. Histological characteristics of kidney biopsy specimens

Histological characteristics	Non-obese group	Intermediate obese group	Obese group
n	36	8	16
Minor glomerular abnormalities	12 (33)	3 (38)	4 (25)
FSGS	15 (42)	3 (38)	10 (63)
Non-IgA mesangial proliferative lesions	3 (8)	2 (25)	1 (6)
Arteriolosclerosis	2 (6)	0	0
Unclassified	4 (11)	0	1 (6)

Values are n (%)

There were no significant differences in the type of lesions among the three groups (P = 0.73; Fisher's exact test).

Table 4. Histological characteristics of kidney biopsy specimens

Variable BMI (kg/m^2)	Control group	Non-obese group <23	Intermediate obese group 23 to <25	Obese group ≥25
n	6	36	8	16
Number of glomeruli	23 ± 5.7	44.1 ± 18.3	55.3 ± 21.2	49.9 ± 16.4
Glomerular diameter (μm)	160 ± 13	181 ± 21	191 ± 21[a]	207.3 ± 20[b]
% of glomerular sclerosis	0 ± 0	13.4 ± 14.6	7.9 ± 3.9	14.4 ± 11.1
% of glomerular FSGS-like lesions	0 ± 0	4.1 ± 7.1	2.2 ± 3.2	6.4 ± 6.9
Mesangial cell proliferation	1.0 ± 0.0	1.1 ± 0.3	1.0 ± 0.0	1.1 ± 0.3
Area of tubular atrophy (%)	0	13.5 ± 14.5	21.3 ± 16.2	22.2 ± 19.8
Area of cell infiltration (%)	0	24.4 ± 19.2	14.4 ± 10.8	22.8 ± 24.3
Area of interstitial fibrosis (%)	0	21.7 ± 20.6	26.9 ± 23.8	28.8 ± 23.9
% thickness of intima in arteriole	0	14.7 ± 22.2	8.8 ± 20.8	14.4 ± 19.1

Values are means ± SD

The Kruskal-Wallis test was employed for this analysis.

Mesangial cell proliferation was scored as follows: 1-3 mesangial cell nuclei (1), 4-5 nuclei (2), 6-7 nuclei (3), or ≥8 nuclei (4).

Percentage thickness of intima in arteriole was calculated as the width of intima/the width of the intima and media × 100.

[a]P < 0.05 vs. the control group; [b]P < 0.01 vs. the control group

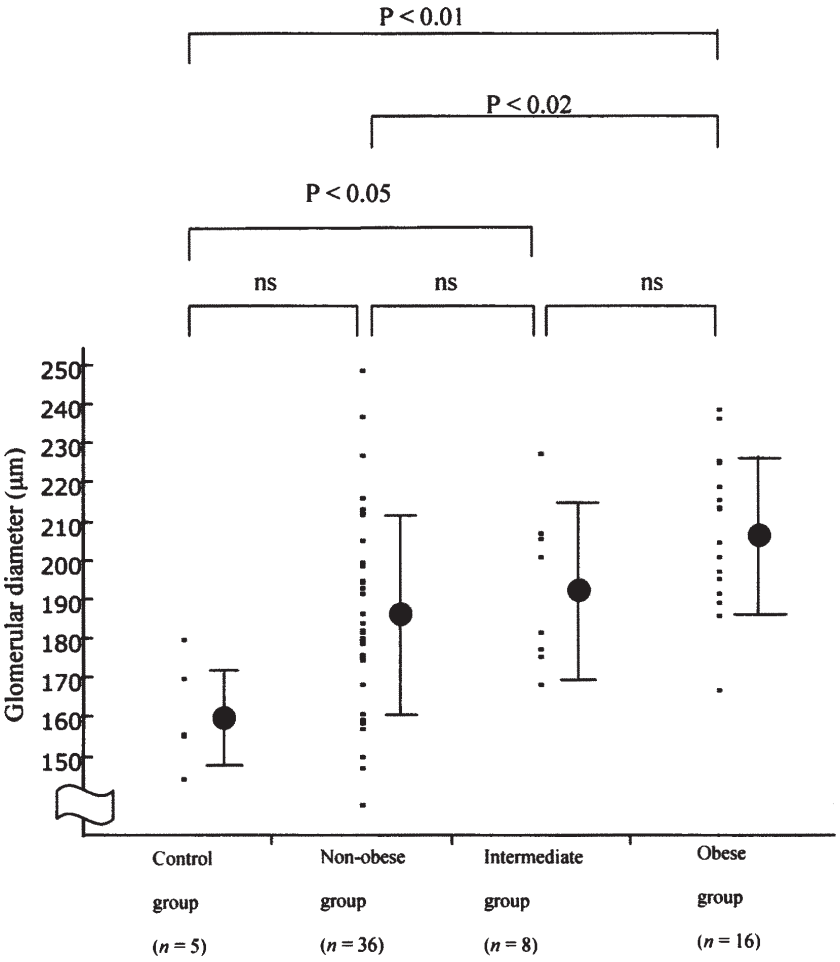

Figure 2. Mean glomerular diameter

The control group consisted of patients with asymptomatic microscopic hematuria and no abnormal findings in their kidney biopsy specimens. The non-obese group, BMI <23 kg/m^2; the intermediate obese group, BMI 23 to <25 kg/m^2; the obese group, BMI ≥25 kg/m^2. Glomerular diameter was significantly different between the control and intermediate obese groups ($P < 0.05$), between the control and the obese groups ($P < 0.01$), and between the non-obese and the obese groups ($P < 0.02$).

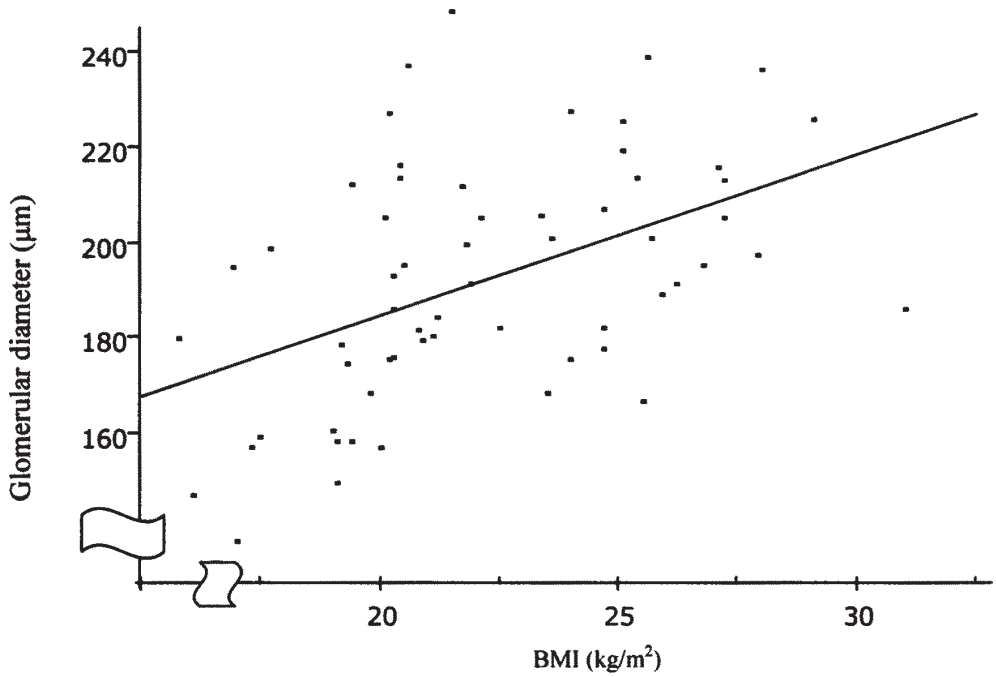

Figure 3. Correlation between the mean glomerular diameter of kidney biopsy specimens and BMI in the total cohort of patients ($r = 0.487$, $P < 0.0001$, n = 60). Regression equation: $y = 11.75 \pm 0.34 \times$ BMI.

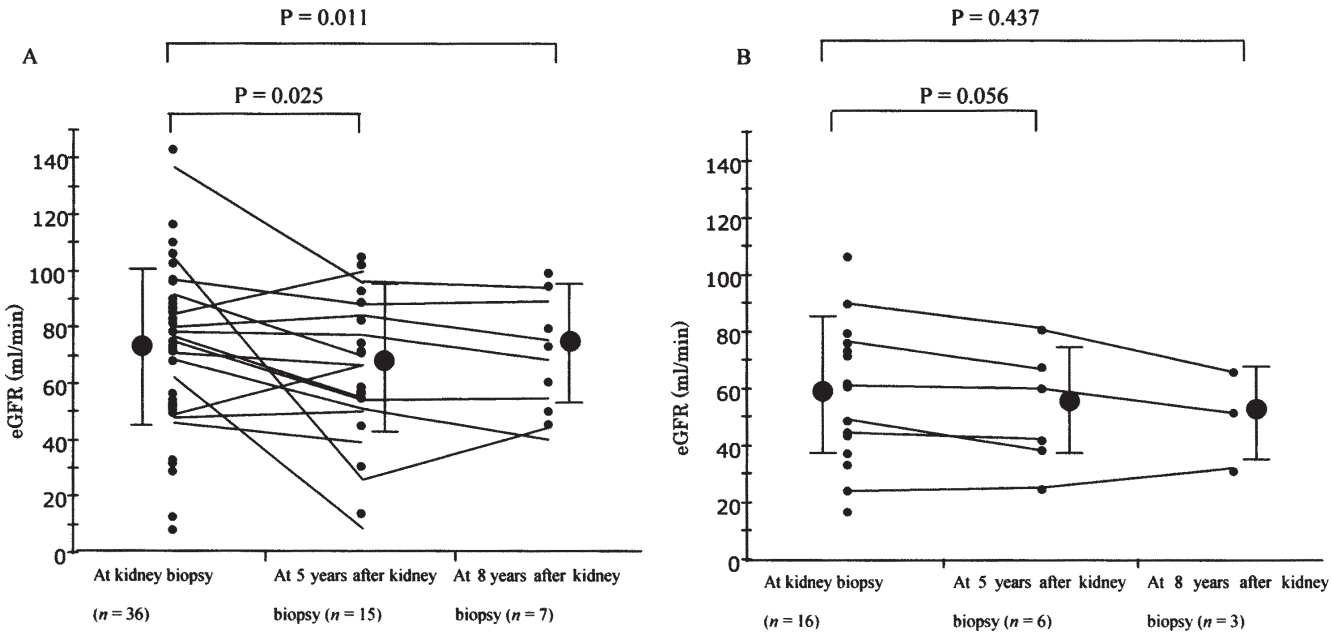

Figure 4. Kidney function, as measured by eGFR in the non-obese (panel **A**) and the obese (panel **B**) patients at kidney biopsy and at 5 and 8 years after biopsy.

Discussion

The definition of ORG, as proposed by Shen et al.[11] consisted of: 1. the presence of obesity; 2. absence of DM; 3. 24-hour urinary protein excretion >0.4 g without gross hematuria or evident microscopic hematuria; 4. pathologic features included glomerulopathy with or without FSGS, and pauci-immune complex deposition; and 5. absence of other underlying renal diseases. In the present study, all of the selected patients satisfied criteria 2-5. Only the obese patients fulfilled criterion 1 and, therefore, met all the proposed criteria for ORG. Consequently, the non-obese patients should receive a diagnosis of idiopathic FSGS, steroid-resistant MCNS, non-IgA GN, or benign nephrosclerosis.

There were no significant differences in the durations of proteinuria and smoking, or systolic/diastolic blood pressure between the non-obese and obese groups. Only the proportion of males was different, with more males in the obese group than in the other groups. Moderate proteinuria was detected in both the non-obese and obese groups, although there was no significant difference between these two groups. Additionally, kidney function, as evaluated by eGFR, was not significantly different between the obese and non-obese groups. Therefore, it seems that routinely recorded clinical indices are unable to distinguish ORG from other pauci-immune glomerular diseases.

The histological analyses of kidney biopsy specimens revealed a distinct difference in glomerular diameter, which was significantly greater in the obese group than that in the non-obese group as shown previously.[12] This increase in glomerular diameter was significantly correlated with BMI in the total cohort of patients. These results suggest that glomerular enlargement, which is associated with BMI, is a distinct histologic characteristic of ORG.

In previous studies, FSGS lesions were detected in 80%,[8] 77%,[10] and 55%[11] of patients with ORG. And the global sclerosis and the segmental sclerosis were seen in 12.5% and 6.3% of glomeruli.[12] In the present study, FSGS lesions were detected in 63% of the patients in the obese group and in 6.4% of their glomeruli. These data indicate that FSGS lesions are common in obese patients, although they affect relatively few glomeruli. Although Kambham et al.[8] reported that 81% of the FSGS lesions in patients with ORG were mixed perihilar and peripheral lesions, the characteristic variant in ORG is still unclear. Indeed, 60% of the FSGS variants were of the tip variant in the obese group, suggesting that this variant is a possible lesion of ORG. Few patients in the obese group had mesangial cell proliferation, which suggests that this lesion may be different from that of ORG. The extent of tubulointerstitial lesions (i.e., tubular atrophy, interstitial cell infiltration, and fibrosis) was moderate in kidney biopsy specimens from the obese group, although it was not significantly different to that in the non-obese group. Therefore, tubulointerstitial lesions are not distinctive of ORG. As arteriolar intima thickening was similar in all three groups, and arteriolosclerotic lesions in the obese

patients were not specific for ORG.

Kambham et al.[8] reported that patients with ORG less frequently experienced doubling of serum creatinine (14.3%) or progression to end-stage kidney disease (3.6%) over a 27-month follow-up compared with patients with idiopathic FSGS (50% and 42%, respectively) over a 39-month follow-up. In the present study, kidney function was relatively stable at 5 and 8 years after kidney biopsy in the obese group, and no patients progressed to end-stage kidney disease. As the prognosis of idiopathic FSGS is better in Japanese patients than in Occidental patients;[13-15] and because the incidence of FSGS lesions in glomeruli is low in obese patients, the prognosis of ORG may also be better in Japanese patients than in Occidental patients.

In conclusion, the most distinct characteristic of ORG was glomerular enlargement, which was significantly correlated with BMI. The tip variant of FSGS may be the main lesion variant associated with ORG. Adequate kidney function may be maintained for many years in patients with ORG, despite moderate proteinuria and reduced kidney function relative to other patients.

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