

Obesity-related glomerulopathy: An emerging epidemic

NEERAJA KAMBHAM, GLEN S. MARKOWITZ, ANTHONY M. VALERI, JULIE LIN,
and VIVETTE D. D'AGATI

Departments of Pathology and Medicine, Columbia University, College of Physicians and Surgeons, New York, New York USA

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Background. We report the first large renal biopsy-based clinicopathologic study on obesity-related glomerulopathy.

Methods. Obesity was defined as body mass index (BMI) >30 kg/m². Obesity-related glomerulopathy (ORG) was defined morphologically as focal segmental glomerulosclerosis and glomerulomegaly (O-FSGS; $N = 57$) or glomerulomegaly alone (O-GM; $N = 14$).

Results. Review of 6818 native renal biopsies received from 1986 to 2000 revealed a progressive increase in biopsy incidence of ORG from 0.2% in 1986–1990 to 2.0% in 1996–2000 ($P = 0.0001$). Mean BMI in ORG was 41.7 (range 30.9 to 62.7). Indications for renal biopsy included proteinuria ($N = 40$) or proteinuria and renal insufficiency ($N = 31$). Seventy-one patients with ORG were compared to 50 patients with idiopathic FSGS (I-FSGS). Patients with ORG were older (mean 42.9 vs. 32.6 years, $P < 0.001$) and more often Caucasian (75% vs. 52%; $P = 0.003$). ORG patients had a lower incidence of nephrotic range proteinuria (48% vs. 66%; $P = 0.007$) and nephrotic syndrome (5.6% vs. 54%; $P < 0.001$), with higher serum albumin (3.9 vs. 2.9 g/dL; $P < 0.001$), lower serum cholesterol (229 vs. 335 mg/dL; $P < 0.001$), and less edema (35% vs. 68%; $P = 0.003$). On renal biopsy, patients with ORG had fewer lesions of segmental sclerosis (10 vs. 39%; $P < 0.001$), more glomerulomegaly (100% vs. 10%; $P < 0.001$), and less extensive foot process effacement (40 vs. 75%; $P < 0.001$). Glomerular diameter in ORG (mean 226 μ) was significantly larger than age- and sex-matched normal controls (mean 168 μ ; $P < 0.001$). Follow-up was available in 56 ORG patients (mean 27 months) and 50 idiopathic FSGS controls (mean 38 months). A total of 75% of ORG patients received angiotensin-converting enzyme (ACE) inhibition or A2 blockade while 78% of the I-FSGS patients received immunosuppressive therapy. ORG patients had less frequent doubling of serum creatinine (14.3% vs. 50%; $P < 0.001$) and progression to ESRD (3.6% vs. 42%; $P < 0.001$). On multivariate analysis, presenting serum creatinine and severity of proteinuria were the only predictors of poor outcome in ORG.

Conclusion. ORG is distinct from idiopathic FSGS, with a lower incidence of nephrotic syndrome, more indolent course, consistent presence of glomerulomegaly, and milder foot pro-

cess fusion. The ten-fold increase in incidence over 15 years suggests a newly emerging epidemic. Heightened physician awareness of this entity is needed to ensure accurate diagnosis and appropriate therapy.

Cross-sectional epidemiologic studies indicate that the prevalence of obesity in the United States and other Western countries has been steadily rising over the past two decades, a trend that has been linked to changing dietary habits and sedentary lifestyle [1–3]. This increased prevalence has been reported in both children and adults, and across diverse ethnic groups [1]. According to the National Health and Nutrition Examination Survey, the prevalence of obesity (defined as body mass index, BMI >30) has increased from 14.1% to 22.5% between 1971 and 1994, and 54.9% of the U.S. population is overweight (BMI >25) [1]. Obese patients are at greater risk to develop sleep apnea, hyperlipidemia, hypertension, coronary vascular disease, insulin resistance and diabetes [4–6].

The renal effects of obesity in experimental animals and humans include both structural and functional adaptations, such as increased glomerular filtration rate, increased renal blood flow, and renal hypertrophy [7, 8]. In 1974, an association between massive obesity and nephrotic-range proteinuria was first reported [9]. Since that time, the development of glomerulomegaly and focal segmental glomerulosclerosis (FSGS) has been linked to massive obesity [8, 10–14]. Most of these associations have been limited to case reports or small autopsy series. Thus, little is known about the overall prevalence of biopsy-documented obesity-related glomerulopathy, its presenting clinical features, morphologic manifestations, or natural history.

The current study was designed to determine the changing biopsy incidence of obesity-related glomerulopathy (ORG) over the past 15 years. To better define the spectrum of clinical and pathologic features of this entity, a cohort of ORG was compared to controls with idiopathic FSGS (I-FSGS). Our findings indicate that ORG is an increasingly prevalent disease that is clinically

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and pathologically distinct from I-FSGS. The differentiating clinicopathologic features of ORG have important implications for patient management and prognosis.

METHODS

All native renal biopsies accessioned in the Renal Pathology Laboratory of Columbia Presbyterian Medical Center from January 1986 to April 2000 were reviewed retrospectively for evidence of ORG. Obesity was defined as a BMI >30, calculated as body weight in kilograms divided by the square of height in meters [1, 15]. ORG was defined morphologically as (1) obesity-associated FSGS with glomerulomegaly (O-FSGS) or (2) obesity-associated glomerulomegaly alone (O-GM). Renal biopsies from obese patients with other underlying conditions that could cause secondary FSGS (such as HIV infection, heroin abuse, solitary kidney, congenital heart disease, sickle cell disease, renal dysplasia, or any other pre-existing renal disease with loss of renal mass) were carefully excluded. Moreover, other defined primary and secondary glomerular diseases including diabetic nephropathy and hypertensive nephrosclerosis occurring in obese patients were eliminated. Of all 6818 native biopsies received during this period, a total of 103 cases met the entry criteria. From this group, 71 cases with adequate clinical information were studied. Because of the limited follow-up, newly diagnosed cases of obesity-related glomerulopathy from the year 2000 were excluded.

Patient charts were reviewed for age, sex, race, and presenting clinical and laboratory features at the time of renal biopsy. From the height and weight at the time of renal biopsy, BMI was calculated. Obesity was defined as BMI >30 kg/m²: BMI 30.0 to 34.9 kg/m², class I obesity; BMI 35.0 to 39.9 kg/m², class II obesity; BMI ≥40 kg/m², class III or "morbid" obesity. The following definitions were used: hypertension (HTN), systolic pressure >140 mm Hg and diastolic pressure >90 mm Hg; nephrotic range proteinuria (NRP), 24-hour urine protein excretion ≥3.5 g; hematuria, presence of >5 red blood cells per high power field on microscopic examination of the urinary sediment; hypoalbuminemia, serum albumin levels ≤3.5 g/dL; hypercholesterolemia, serum cholesterol >200 mg/dL; nephrotic syndrome, the combination of NRP, hypoalbuminemia and edema; and renal insufficiency, serum creatinine >1.2 mg/dL on two separate determinations. Creatinine clearances calculated from 24-hour urine collections were available in 58 patients. Clearances were adjusted for body surface area using height and weight according to the following formula: [(height in centimeters)(weight in kilograms)/3600]^{1/2} [16, 17]. Presenting clinical and laboratory features were compared to a well-characterized historical control group of 50 patients with I-FSGS of the classic type,

(excluding cellular and collapsing variants) diagnosed from 1980 to 1992.

Renal biopsies for the study cohort and controls were processed for light microscopy, immunofluorescence (IF) and electron microscopy (EM) according to standard techniques. At least 11 serial sections (3 μm thick) were stained with hematoxylin and eosin, periodic-acid Schiff (PAS), Masson's trichrome and Jones methenamine-silver stains (JMS). Routine IF was performed on 3 μm cryostat sections using polyclonal FITC-conjugated antibodies to IgG, IgM, IgA, C3, C1q, κ, λ, fibrinogen and albumin (Dako Corporation, Carpinteria, CA, USA). In 61 of 71 ORG cases, adequate glomerular tissue was available for EM.

Juxtaglomerular apparatus (JGA) hyperplasia was defined as >8 nuclei per cross section of JGA [18]. Tubular atrophy, interstitial fibrosis and inflammation were graded semiquantitatively on a scale of 0 to 3+ based on the % cortical area affected: 0 = absent; 1+ = 1–25%; 2+ = 26–50% and 3+ > 50%. Arteriosclerosis and arteriolosclerosis were graded as follows: 0 = absent; 1+ = mild; 2+ = moderate; 3+ = severe. The intensity of staining by immunofluorescence was graded on a scale of trace (+/–) to 3+. The percentage of foot process effacement was estimated based on examination of all nonsclerotic glomerular capillaries in all fields.

Measurement of glomerular diameter was performed using a light microscopic eyepiece with built-in micrometer (Olympus Scientific, Tokyo, Japan). The conversion factor for each objective was calibrated against a standard by the manufacturer. Four levels of biopsy tissue (PAS and JMS stains) were studied in each case. All glomeruli cut at or near the hilus were measured. Two perpendicular diameters extending between the farthest glomerular basement membrane points were measured per glomerulus. The mean glomerular diameter (μm) was calculated from a total of 5 to 30 (mean 15) glomeruli examined per case. Glomerular diameter was compared to that of 21 age- and sex-matched normal controls obtained from percutaneous renal biopsies of patients with isolated asymptomatic hematuria or subnephrotic proteinuria who had no evidence of glomerular disease by light microscopy, IF, or EM.

The following clinical and laboratory data at follow-up were analyzed for the group with ORG and I-FSGS: Therapy directed to renal disease or obesity (including weight reduction, sleep apnea therapy, angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor antagonists, steroids or other immunosuppressive agents) was recorded for each patient. Measures of serum creatinine, 24-hour urine protein, and body weight at last available follow-up were analyzed. Life-table analysis was performed using the outcome points of doubling of serum creatinine and end-stage renal disease.

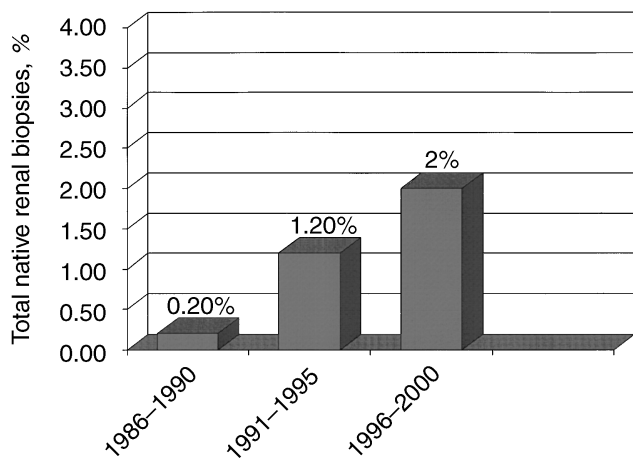


Fig. 1. The increased incidence of obesity-related glomerulopathy (ORG) is plotted as a percentage of total native renal biopsies received over a 15-year period.

Statistical analysis

Statistical analysis was performed by exact statistical inference using the following nonparametric methods: Fisher's exact test, the Mann-Whitney *U* test, and the Wilcoxon signed ranks test, as appropriate. The Monte Carlo approximation method was used where the statistical package could not solve the analysis by exact methodology within 15 minutes or iteration processing time. SPSS® 10.0.5 was used to perform the analysis. Multivariate analysis was performed by logistic regression analysis. Patient and renal outcome survival analysis was performed by the method of Kaplan and Meier with statistical comparison by the log rank test. A multivariate analysis for predictors of outcome was performed by Cox regression analysis. Statistical significance was assumed at $P < 0.05$.

RESULTS

Biopsy incidence of obesity-related glomerulopathy

The biopsy incidence of ORG was determined for the 15-year period of January 1986 to April 2000 (Fig. 1). Among the 103 cases of ORG identified from 1986 to 2000, only two cases (2 of 956 native kidney biopsies; 0.2%) were identified from January 1986 to December 1990; 24 cases (24 of 2013; 1.2%) were identified from January 1991 to December 1995; and 77 cases (77 of 3849; 2%) were identified from January 1996 to April 2000. This represents a ten-fold increase in biopsy incidence of ORG over 15 years ($P = 0.0001$).

Clinical features at presentation

The mean age of patients at the time of biopsy diagnosis of ORG was 42.9 years (range 8–71 years; Table 1). The youngest patients in the study group included an

8-year-old girl [height 4.0 ft (121.9 cm), weight 190 lbs (86.4 kg)] and three patients in their second decade of life; the oldest patients included seven in their sixth decade and one in his seventh decade. The patients' weights ranged from 180 lbs to 410 lbs (81.8 kg to 186.4 kg). The mean BMI was 41.7 kg/m² (range of 30.9 to 62.7); 38 patients had BMI >40 kg/m² and 33 had BMI <40 kg/m². The male-to-female ratio was 44:27 (1.6). The majority of patients were Caucasian (75%), followed by African American (21%) and Hispanic (4%). Nine patients had history of diabetes mellitus (12.7%) for a mean duration of 4.8 years (range 0.5 to 26 years). However, none of these patients had renal biopsy findings of diabetic nephropathy. Forty-four patients had a prior history of hypertension of a mean 9 years' (range from 0.2 to 40 years) duration. Eight patients carried a diagnosis of obstructive sleep apnea syndrome prior to renal biopsy; however, sleep apnea studies were not performed on the majority of patients.

The indications for renal biopsy were isolated proteinuria in 40 patients (56%) and proteinuria and renal insufficiency in 31 patients (44%). The mean serum creatinine at presentation was 1.5 mg/dL (range 0.6 to 6.3 mg/dL). The creatinine clearance (C_{Cr}) was available in 58 patients and the mean value was 113 cc/min (range 20 to 240 cc/min). The mean C_{Cr} adjusted for BSA was 82.9 mL/min/1.73 m² (range 13 to 186). Twenty-four of 58 patients (41.4%) had $C_{Cr} >130$ cc/min. Based on an adjusted C_{Cr} , 8 of 58 patients (13.8%) had a $C_{Cr} >130$ mL/min/1.73 m² and 32 patients (55%) had $C_{Cr} <75$ mL/min/1.73 m². The mean 24-hour urine protein was 4.1 g (range 1 to 32 g). Although 34 patients (48%) had nephrotic-range proteinuria at presentation, only 4 patients (5.6%) had nephrotic syndrome. The mean serum albumin level was 3.9 g/dL (range 1.5 to 5.0 g/dL) and only ten patients (14%) had hypoalbuminemia. Twenty-five patients (35%) had pedal edema at presentation. The serum cholesterol levels ranged from 152 to 303 mg/dL (mean 229 mg/dL) and 38 patients (54%) were hypercholesterolemic. Microhematuria was documented in 15 patients.

When the presenting clinical features of the ORG group were compared with I-FSGS controls, many significant differences were found (Table 1). Patients with ORG were more likely to be Caucasian (74.6 vs. 52%; $P = 0.003$) and tended to be older (mean age 42.9 vs. 32.6 years; $P < 0.001$) compared to historical controls with I-FSGS. Although nearly half of the ORG patients presented with nephrotic-range proteinuria (48% vs. 66%; $P = 0.007$), the incidence of pedal edema (35% vs. 68%; $P = 0.003$) and nephrotic syndrome (5.6% vs. 60%; $P < 0.001$) was significantly lower in the ORG group. Correspondingly, the mean serum albumin levels were higher (3.9 g/dL vs. 2.9 g/dL; $P < 0.001$) and the mean 24-hour urine protein excretion was lower (4.1 g vs. 6.9 g; $P = 0.002$) than in I-FSGS controls. The mean

Table 1. Clinical parameters and pathological findings in patients with ORG, O-FSGS and I-FSGS

Parameter	ORG (N = 71)	O-FSGS (N = 57)	I-FSGS (N = 50)	ORG vs. I-FSGS (P value)	O-FSGS vs. I-FSGS (P value)
Mean age at presentation years	42.93	43.82	32.57	<0.001	<0.001
Sex male:female	44:27	37:20	25:25	0.186	0.092
Race/ethnicity N (%)				0.003	0.018
Caucasian	53 (74.6)	40 (70.2)	26 (52)		
African American	15 (21.1)	14 (24.5)	11 (22)		
Hispanic	3 (4.2)	3 (5.3)	11 (22)		
Other	0	0	2 (4)		
HTN + N (%)	44 (62)	37 (64.9)	28 (56)	0.574	0.428
Mean S _{Cr} at biopsy mg/dL	1.47	1.55	1.96	0.8	0.903
Proteinuria				0.007	0.012
Non-nephrotic proteinuria N (%)	37 (52.1)	30 (52.6)	17 (34)		
Nephrotic range proteinuria N (%)	34 (47.9)	27 (47.4)	33 (66)		
Nephrotic parameters					
Nephrotic syndrome N (%)	4 (5.6)	4 (7)	27 (54)	<0.001	<0.001
Mean 24-hour urine protein g	4.09	4.24	6.89	0.002	0.004
Mean serum albumin g/dL	3.87	3.8	2.9	<0.001	<0.001
Mean serum cholesterol mg/dL	229.2	231.65	335.13	<0.001	<0.001
Presence of edema N (%)	25 (35)	23 (40.4)	34 (68)	0.003	0.01
Pathology					
Mean % global sclerosis	20%	25%	18%	0.423	0.027
Mean % segmental sclerosis	10%	12%	39%	<0.001	<0.001
% of cases with glomerulomegaly	100%	100%	10%	<0.001	<0.001
Mean TA/IF (grade 0–3)	mild (1.08)	mild (1.26)	mild (1.22)	0.238	0.912
Mean arteriosclerosis (grade 0–3)	mild (1.34)	mild (1.42)	mild (0.98)	0.032	0.014
Foot process fusion	40%	41%	75%	<0.001	<0.001

Abbreviations are: ORG, obesity-related glomerulopathy; FSGS, focal segmental glomerulosclerosis; O-FSGS, obesity-related FSGS; I-FSGS, idiopathic FSGS; HTN, hypertension; TA/IF, tubular atrophy and interstitial fibrosis. Terms are defined in the text.

serum cholesterol level, although elevated, was significantly lower than in I-FSGS patients (229 mg/dL vs. 335 mg/dL; $P < 0.001$). Although patients with ORG were more likely to be hypertensive (62% vs. 56%) and had slightly lower mean serum creatinine at biopsy (1.47 vs. 1.96 mg/dL), these differences were not statistically significant.

Because the ORG group contained some patients with glomerulomegaly alone (O-GM) as well as the larger group with glomerulomegaly and FSGS (O-FSGS), comparative analyses were also performed for O-FSGS patients ($N = 57$) versus I-FSGS controls ($N = 50$). As shown in Table 1, the differences were similar to those observed between the ORG and I-FSGS groups. Also, within the study group of ORG, no statistically significant differences were found between those with O-FSGS and O-GM with respect to any clinical parameter listed in Table 1 (data not shown).

Renal biopsy findings

Light microscopic findings. Among the 71 cases of ORG, 57 had lesions of FSGS with glomerulomegaly (O-FSGS) and 14 cases had glomerulomegaly alone (O-GM). By light microscopy, the total number of glomeruli sampled ranged from 5 to 30 (mean 6.4 in O-GM; mean 14.2 in O-FSGS).

In the O-FSGS group, the percentage of globally sclerotic glomeruli ranged from 0% to 73% (mean 25%)

and the percentage of segmentally sclerotic glomeruli ranged from 3% to 50% (mean 12%; Table 1). All cases had lesions of segmental sclerosis of the “classic” or usual type, characterized by segmental obliteration and solidification of glomerular capillary lumina by increased matrix, forming expansile scars, often associated with inframembranous hyaline, endocapillary foam cells and Bowman’s capsular adhesions (Fig. 2 A–C). In some cases, the hypertrophied podocytes overlying the lesions were segmentally detached from the glomerular basement membranes and aligned over the sclerotic segment, forming a cellular “cap.” In addition to these classic lesions, four cases also displayed focal cellular lesions of FSGS involving from 4 to 17% of glomeruli, one case had a glomerular tip lesion, and a single case had one glomerulus with global collapse of the tuft and overlying prominent podocyte hyperplasia [19–21]. Of note, 2 of the 4 patients with full nephrotic syndrome had lesions of cellular or collapsing FSGS.

On analysis of the distribution of segmental lesions relative to the vascular pole, 11 O-FSGS cases (19%) had exclusively perihilar lesions. In the remainder (81%), the lesions were in mixed perihilar and peripheral locations. Within the O-FSGS group, 16 cases (28%) also had one or more glomeruli with slightly increased matrix about the vascular pole, with or without associated hyalinosis; however, the size of these perihilar lesions did not reach the threshold for diagnosis of segmental sclerosis.

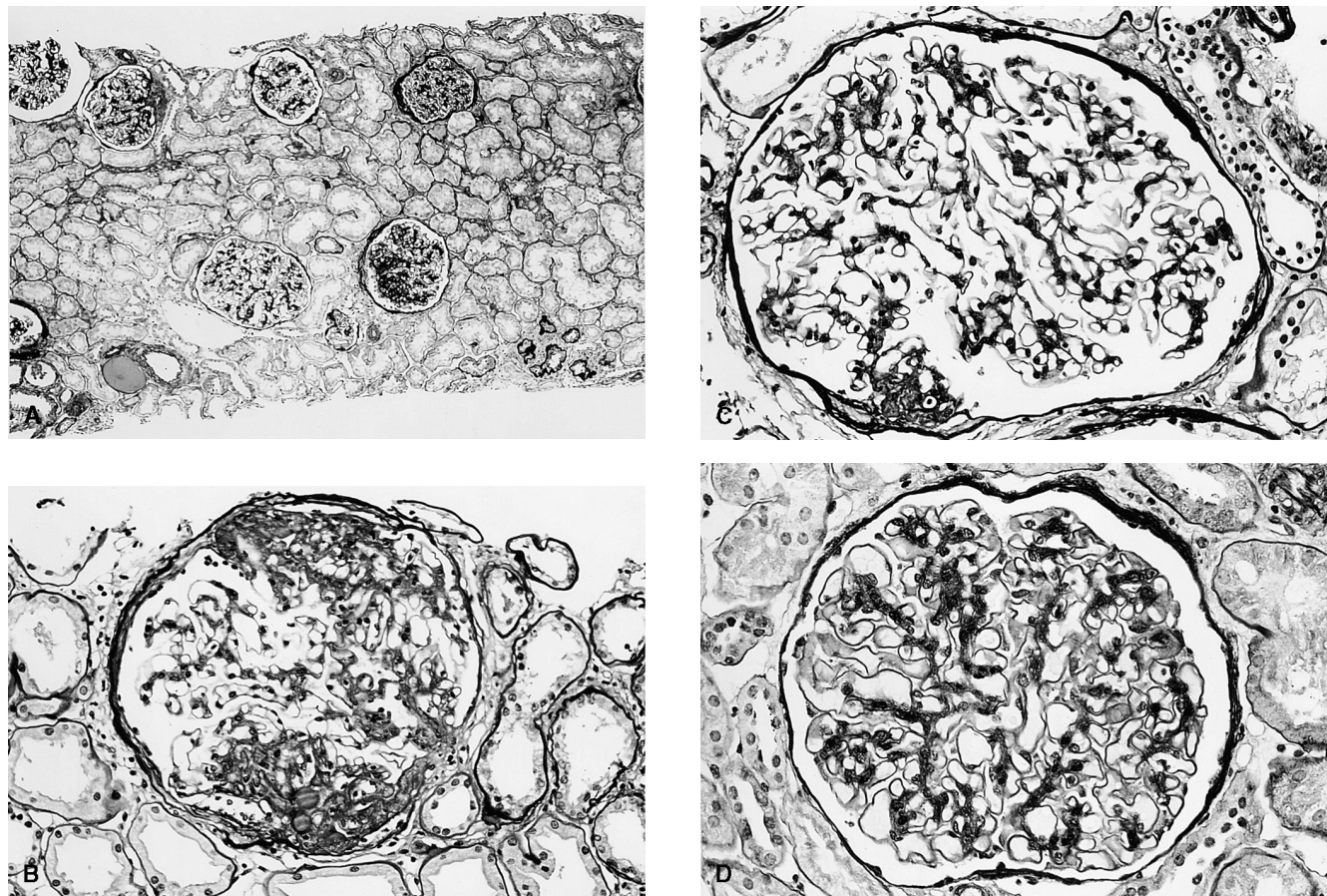


Fig. 2. (A) A low power view of ORG shows focal segmental glomerulosclerosis and glomerulomegaly. There is minimal focal tubular atrophy (PAS, $\times 100$). (B) A hypertrophied glomerulus contains two discrete lesions of segmental sclerosis, one in the perihilar region and one in the peripheral tuft, with hyalinosis and adhesion to Bowman's capsule (PAS, $\times 250$). (C) A case of ORG with a massively hypertrophied glomerulus containing a peripherally situated discrete lesion of segmental sclerosis (PAS, $\times 250$). (D) A glomerulus with mild "diabetoid" changes characterized by mild mesangial sclerosis, mild diffuse glomerular basement membrane thickening, and glomerulomegaly from a patient with ORG and no clinical history of diabetes mellitus (PAS, $\times 300$). (E) By electron microscopy, diffuse glomerular basement membrane thickening and mild mesangial sclerosis are seen in this case of ORG without clinical evidence of diabetes ($\times 2,500$). (F) A typical electron microscopic view of a glomerulus in ORG shows minimal foot process effacement despite nephrotic range proteinuria ($\times 2,500$). (G and H) There is marked glomerular hypertrophy in ORG (G) compared to an age- and sex-matched normal control (H) (PAS, $\times 300$).

In O-FSGS, tubular atrophy and interstitial fibrosis was typically mild (mean 1.26+), as was interstitial inflammation (mean 0.8+). No tubular microcysts or significant tubular degenerative/regenerative changes were observed. The arteriosclerosis (often with associated hyalinosis) ranged from mild to moderate (mean 1.42+).

In the O-GM group, by definition no lesions of global or segmental glomerulosclerosis were identified. However, three cases (21%) had slightly accentuated matrix about the vascular pole, as noted in some cases of O-FSGS. The tubular atrophy and interstitial fibrosis in this group were minimal (mean 0.36+; range 0 to 1+) and significantly less than in O-FSGS ($P < 0.001$). The degree of arteriosclerosis (mean 1.0+) was not significantly different from that of the O-FSGS group ($P = 0.1$).

Another histologic feature noted in some ORG pa-

tients was the presence of focal "diabetoid" changes in the form of mild focal mesangial sclerosis or mild focal thickening of glomerular basement membranes and tubular basement membranes (Fig. 2D). One or more of these features were present in 32 (45%) cases. Six of these patients had history of non-insulin-dependent diabetes mellitus (NIDDM) and one had documented glucose intolerance. However, because these seven cases had exclusively glomerular basement membrane thickening, without mesangial sclerosis, they did not meet diagnostic criteria for diabetic nephropathy.

Juxtaglomerular apparatus (JGA) hyperplasia was seen in 14 (19.7%) of ORG cases, of which only 5 patients had a history of hypertension (of < 2 years' duration in four cases and of 10 years' duration in one case). Interstitial foam cells were seen in 7 (10%) cases, 5 of whom had nephrotic range proteinuria.

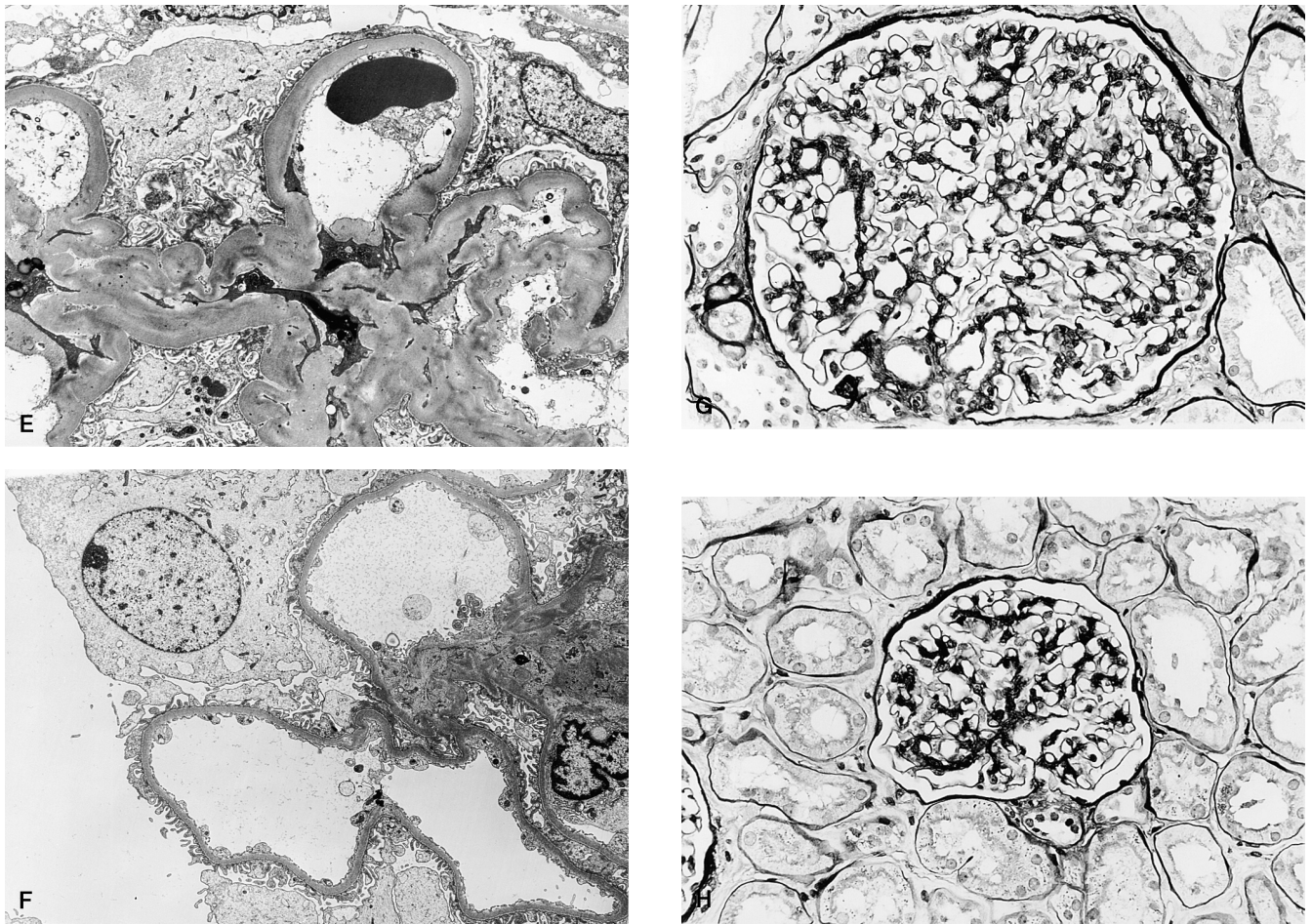


Fig. 2. (continued)

Immunofluorescence findings. In O-FSGS, there was focal and segmental or global staining of the glomerular tuft with antisera to IgM and C3 (1 to 2+), corresponding to areas of glomerulosclerosis. More generalized mesangial staining for IgM (1+) was also common. Fifteen ORG cases had trace to 1+ linear staining of glomerular basement membranes with antisera to IgG and albumin, 4 of whom also had similar staining in the tubular basement membranes. Four of these 15 patients were diabetic (1.5 to 26 years' duration) and one had documented glucose intolerance.

Electron microscopic findings. Lesions of segmental glomerulosclerosis demonstrated segmental solidification of the tuft by basement membrane material and inframembranous hyaline. Overlying these areas, there was frequent podocyte detachment and capping, with intervening layering of neomembrane material. Mild podocyte hypertrophy and intracytoplasmic protein resorption droplets were identified in a few cases. Few small electron dense deposits were confined to the mesangial and paramesangial areas in 12 patients, corresponding

to the mesangial positivity for IgM observed by immunofluorescence. In 25 cases of O-FSGS and 9 cases of O-GM, the glomerular basement membranes were mildly focally thickened (Fig. 2E). Overlying patent capillaries, the podocytes had preserved primary processes with little if any microvillous transformation and with variable, but generally modest, foot process fusion (mean 40%, range 10 to 100%; Fig. 2F).

Glomerular diameter. Mean glomerular diameter of ORG patients was $226 \pm 24.6 \mu\text{m}$ (range 172 to 300 μm), a value significantly greater than that of age- and sex-matched normal controls (mean $168 \pm 12 \mu\text{m}$; range 138 to 186 μm ; $P < 0.001$; Fig. 2 G, H). The individual values are plotted in Figure 3.

Comparative morphologic findings. On statistical analysis, the O-FSGS group had significantly fewer lesions of segmental sclerosis than controls with I-FSGS (12% vs. 39%; $P < 0.001$). The percentage of globally sclerotic glomeruli was significantly higher in O-FSGS (but not ORG) than in I-FSGS (25% vs. 18%; $P = 0.027$). The incidence of glomerulomegaly, a defining

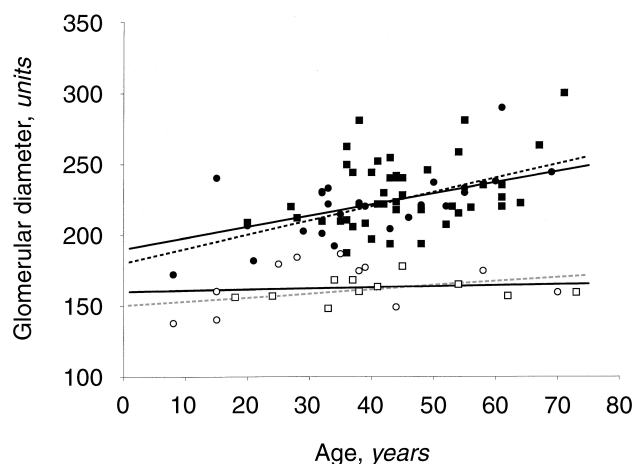


Fig. 3. Glomerular diameter is plotted for ORG and for normal age- and sex-matched controls. Symbols are: (■, ●) ORG male and female, respectively; (□, ○) control male and female respectively; top solid and dashed lines are mean ORG male and female, respectively; bottom solid and dashed lines are mean control male and female, respectively.

feature of ORG, was significantly higher in ORG versus I-FSGS (100% vs. 10%; $P < 0.001$). Patients with ORG tended to have more severe arteriosclerosis compared to I-FSGS (1.34+ vs. 0.98+; $P = 0.03$). However, the severity of tubular atrophy and interstitial fibrosis was not statistically different. There was significantly less foot process effacement in ORG (mean 40%, range 10 to 100%) than in I-FSGS (mean 75%, range 30 to 100%; $P < 0.001$).

Comparative multivariate analysis between ORG and I-FSGS

The parameters found to be significantly different by univariate analysis between the groups (Table 1) were analyzed by multivariate analysis using logistic regression. When ORG was compared to I-FSGS, the only parameters that were independently significant were serum albumin ($P < 0.001$) and age ($P = 0.032$). When the O-FSGS and I-FSGS groups were compared, again, serum albumin ($P < 0.001$) and age ($P = 0.018$) were the only independently significant variables. These results are consistent with the observation that the major distinguishing feature between ORG and I-FSGS is the presence of full nephrotic syndrome in I-FSGS, as reflected by the severity of hypoalbuminemia.

By logistic regression analysis, both the type of FSGS (ORG vs. I-FSGS) and the 24-hour urinary protein excretion were significant and independent predictors of hypoalbuminemia ($P = 0.002$ for the type of FSGS, with I-FSGS being the stronger predictor of hypoalbuminemia and $P < 0.001$ for 24-hour urine protein excretion). The 24-hour urine protein and serum albumin were both significant and independent predictors of hypercholesterolemia (cholesterol >300 mg/dL), but the type of

FSGS (ORG vs. I-FSGS) was not predictive of hypercholesterolemia.

Therapy and clinical outcome

Of the 71 ORG patients, 15 patients (including 9 O-FSGS and 6 O-GM) were lost to follow-up (Table 2). Thirty-four of the remaining 56 (61%) patients were treated with either ACE-I or angiotensin II receptor antagonists. Four additional patients (7%) were treated with both ACE-I and steroids, one of whom presented with nephrotic syndrome and had features of cellular FSGS on biopsy. Treatment was not statistically different between the O-FSGS and O-GM groups.

Follow-up was available on all 50 I-FSGS patients: 39 patients (78%) received immunosuppressive therapy, of whom 21 received steroids alone and the remainder received steroids plus either cyclophosphamide (6), or cyclosporine (8), or both sequentially (4).

The mean follow-up was 27 months (range 2 to 117 months) for the ORG group and 39 months (range 1 to 140 months) for the I-FSGS controls ($P = 0.049$). Eight patients with ORG (14.3%) had doubling of serum creatinine and two of these patients (3.6%) progressed to ESRD requiring renal replacement therapy. By contrast, in the I-FSGS controls, 25 (50%) had doubling of serum creatinine on follow-up, of whom 21 patients (42%) required renal replacement therapy ($P < 0.001$). The mean time to reach this end point was longer for ORG patients compared to I-FSGS patients (93 vs. 63 months; $P = 0.023$; Fig. 4). Among the 8 ORG patients who reached doubling of serum creatinine, all belonged to the O-FSGS subgroup, 2 presented with nephrotic syndrome, and 1 had collapsing features on biopsy. Four of these 8 patients had been treated with ACE-I alone and 4 received no therapy. There was no significant difference in renal functional outcome of treated and untreated patients, as well as those treated with ACE-I alone versus a combination of ACE-I and steroids. When patients were dichotomized for BMI less than or greater than 40, no differences in outcome were identified.

Follow-up data on proteinuria was available in 26 patients with ORG, of whom 18 were receiving ACE-I. Eighteen patients (69.2%) had a decline in 24-hour urine protein. Among these 26 patients, the mean 24-hour urine protein declined from 3.92 to 2.55 g/day ($P = 0.011$). A mean reduction in urine protein excretion of 1.0 g/day was found in the 18 patients treated with ACE-I. Of the 4 patients receiving steroid therapy, 3 had follow-up data on proteinuria and 2 had an improvement in urine protein excretion (one with reduction in urine protein excretion from 13.0 to 1.4 g/day at 6 months of follow-up and the other with reduction from 2.0 to 0.6 g/day at 98 months, both with stable renal function). However, because so few patients were treated with ste-

Table 2. Treatment and outcome data in patients with ORG, O-FSGS and I-FSGS

Parameter	ORG (N = 71)	O-FSGS (N = 57)	I-FSGS (N = 50)	ORG vs. I-FSGS (P value)	O-FSGS vs. I-FSGS (P value)
N of cases with follow-up	56	48	50		
Mean length of follow-up <i>months</i>	27	27	39	0.049	0.045
Treatment					
ACE-I or ARB without steroids	34	29	0		
ACE-I or ARB + steroids	4	4	0		
Steroids alone	0	0	21		
Steroids + cytotoxic agents	0	0	18		
None	18	15	11		
Renal survival data					
Doubling of S _{Cr} (or ESRD)	8 (14.3%)	8 (17%)	25 (50%)	<0.001	<0.001
ESRD	2 (3.6%)	2 (4%)	21 (42%)	<0.001	<0.001
Mean renal survival time <i>months</i>	93	91	63	0.023	0.049

Abbreviations are in Table 1 legend. Other abbreviations are: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockade; S_{Cr}, serum creatinine; ESRD, end-stage renal disease.

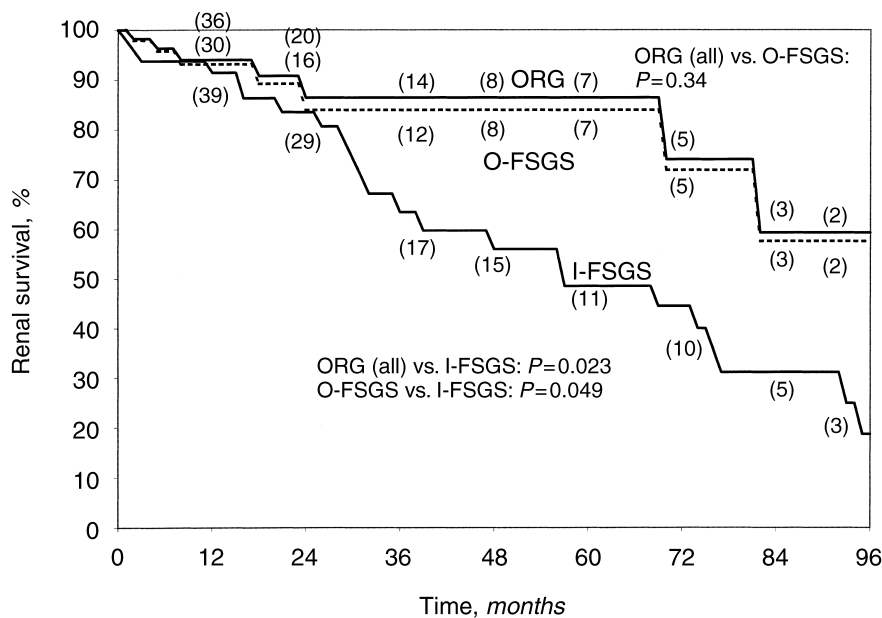


Fig. 4. Renal survival (endpoints defined as doubling of serum creatinine or ESRD) over time in ORG, O-FSGS, and control I-FSGS. Analysis by the method of Kaplan and Meier with comparison by the log rank test. Symbols are: (bottom solid line) I-FSGS; (top solid line) ORG (all); (dotted line) O-FSGS. ORG (all) vs. O-FSGS, $P = 0.34$; ORG (all) vs. I-FSGS, $P = 0.023$; O-FSGS vs. I-FSGS, $P = 0.049$.

roids, any potential effect could not be analyzed statistically.

Five patients had significant weight loss ranging from 10% to 36% of their original weight over the 19 to 35 months of available follow-up. Four of these patients did not receive any other specific therapy. In all four cases, proteinuria declined by at least 50% and, in one case by 75%. The renal function remained normal or stable in all four.

Two patients with ORG died within 6 months of renal biopsy despite stable renal function. Causes of death were congestive heart failure in a 54-year-old male and sleep apnea in an 8-year-old girl.

Multivariate survival analysis was performed in ORG using all the demographic, clinical, laboratory, and pathologic parameters listed in Table 1 as well as the

following: weight, BMI, duration of hypertension, presence of diabetes, hematuria, follow-up time, ACE-I treatment, steroid treatment, histologic subtype of segmental lesion (classic, cellular, collapsing), location of segmental lesion (perihilar vs. peripheral), and glomerular diameter. Only two factors were found to be predictive of poor outcome in the ORG group: presenting serum creatinine ($P = 0.003$) and severity of proteinuria at presentation ($P = 0.022$).

DISCUSSION

The prevalence of obesity is on the rise in United States and in other industrialized nations and has reached epidemic proportions [1–3]. Our findings of a tenfold increase in the biopsy incidence of this condition

over the past 15 years are congruent with epidemiologic data documenting a sharply increasing prevalence of obesity in the general population. Because the indications for renal biopsy (nephrotic range proteinuria, with or without renal insufficiency) have not changed appreciably over this time period, we interpret our increasing biopsy incidence of ORG to reflect the increase in the incidence of obesity. Previous reports of ORG have been in patients with massive obesity [8, 10–14]. Our study reveals, to our knowledge for the first time, that even patients with submorbid (class I and II) obesity, who constituted 46% of the study group, can develop ORG that is clinically and morphologically indistinguishable from that seen in morbid obesity.

Our study found a significantly higher incidence of ORG in Caucasians compared to our biopsy population with I-FSGS ($P = 0.03$). We can only speculate about the reasons underlying these racial differences. These data may reflect genetically determined risk factors for ORG as well as socioeconomic determinants that influence the rate of referral of obese patients of different races to a nephrologist.

The overall renal effects of obesity include elevated GFR, elevated renal blood flow, and renal hypertrophy. The association of proteinuria with massive obesity was first reported in 1974 [9]. The prevalence of proteinuria in obese patients has been addressed in several cross-sectional studies of large populations of obese patients. Among 257 obese patients screened at Brigham and Women's Hospital, only 4 (0.015%) had dipstick proteinuria of 2+ or greater, a value much lower than the prevalence of diabetes (15%) and hypertension (23%) in the same population (abstract; Goldszer et al, *Kidney Int* 25:165A, 1984). However, in another study of 207 nondiabetic obese patients, 25 (12%) had documented microalbuminuria [22]. In the 1980's several case reports and small autopsy series of ORG appeared [8, 11, 13]. Our study provides the first large comparative biopsy series on this entity.

Our data indicate that the presentation of ORG is typically one of nephrotic range-proteinuria (48%) or sub-nephrotic proteinuria (52%), accompanied by renal insufficiency in nearly half (44%). Although nearly half of patients had nephrotic range proteinuria, hypoalbuminemia was present in only 14% and only 5.6% of patients had full nephrotic syndrome. This presentation stands in sharp contrast to controls with I-FSGS, of whom 54% had nephrotic syndrome (a value similar to the 70% rate of nephrotic syndrome estimated by Korbet in a compilation of series of adult I-FSGS) [23]. Although 54% of ORG patients had hypercholesterolemia, correlating with the increased prevalence of hyperlipidemia in obesity, the mean serum cholesterol (229 mg/dL) was significantly lower than that in I-FSGS (335 mg/dL; $P < 0.001$). These results are similar to those of Praga and

Kassiske, and likely reflect fundamental differences in the pathophysiology of this secondary form of FSGS [12, 24, 25]. The reason why patients with ORG have a lower incidence of nephrotic syndrome compared to I-FSGS may relate to differences in the severity of podocyte injury, in the severity and selectivity of proteinuria, and in the ability of the tubules to reabsorb and catabolize the filtered protein. The lower fractional excretions of β_2 -microglobulin (which competes with albumin for tubular uptake) and *N*-acetyl β -glucosaminidase (a marker of tubular injury) observed in patients with nephrotic range proteinuria compared to those with nephrotic syndrome suggest differences in tubular overload and resulting cellular injury. The urinary losses of protein in ORG may be insufficient to stimulate the hepatic synthesis of lipoprotein typically observed in I-FSGS [24, 25]. Life table analysis indicates that the course of ORG is indolent with less frequent progression to ESRD. Although our historical controls with I-FSGS had significantly longer follow-up, life table analysis corrects for these differences. The favorable prognosis of ORG despite a lack of treatment with steroids in all but four patients provides further proof that ORG is a distinct and separable clinicopathologic entity.

Although both ORG and I-FSGS manifest lesions of focal segmental glomerulosclerosis, there are distinguishing morphologic features. As a group, ORG has a lower percentage of glomeruli affected by segmental sclerosis, suggesting a milder and more slowly progressive disease. Although routine histologic sections are known to underestimate the total number of glomeruli affected by focal segmental sclerosis, these differences were obtained by examination of standardized numbers of tissue sections in the two groups [26]. Ultrastructurally, the degree of foot process effacement was also less severe (mean 40% vs. 75%, $P < 0.001$), suggesting a different pathomechanism of podocyte injury. However, because the range of % foot process fusion in each group was wide (10 to 100% for ORG and 30 to 100% for I-FSGS), the percentage of foot process fusion cannot differentiate ORG from I-FSGS with certainty. Glomerulomegaly was consistently observed in ORG (100%) compared to only 10% of patients with I-FSGS, underscoring the importance of hyperfiltration mechanisms in its pathogenesis. These differences in the incidence of glomerulomegaly cannot be explained by loss of renal mass as a stimulus to hyperfiltration, because the degree of glomerulosclerosis and chronic tubulointerstitial disease, as well as the presenting serum creatinine levels, were higher in the I-FSGS group. Patients with ORG also tended to have more severe arteriosclerosis ($P = 0.03$), despite a similar incidence of hypertension as I-FSGS. These differences may be related to the older age and greater risk of coronary vascular disease in ORG.

Of interest, only 5 (7.0%) cases of ORG had cellular or

collapsing lesions. Although our study design precluded comparisons with I-FSGS because our control group was restricted to cases with classic FSGS, this value is far lower than the 34% incidence of cellular lesions in I-FSGS described by Schwartz and Lewis [20]. ORG cases had little podocyte hypertrophy or hyperplasia, similar to the findings reported by Verani in an autopsy series of 22 obese patients [14]. The ability to determine the location of the sclerotic lesions within the three-dimensional topography of the tuft in routine histologic sections is limited; nonetheless, our findings that 19% of cases had exclusively perihilar sclerosis and 28% had accentuated matrix about the vascular pole are in agreement with the predilection to perihilar sclerosis reported by Verani in ORG kidneys [14]. This tendency for sclerosis to involve the vascular pole may be related to the higher filtration pressure of the proximal glomerular capillary network due to its lower oncotic pressure. The limited tissue sampling in percutaneous renal biopsies did not permit evaluation of the distribution of segmental lesions with respect to the corticomedullary junction. However, an autopsy series has shown that, unlike I-FSGS, there is no predilection for the corticomedullary junction in O-FSGS [14].

Importantly, our series is the first, to our knowledge, to report that ORG may manifest with glomerulomegaly alone, in the absence of FSGS. The single report of massive obesity and nephrotic proteinuria with “normal renal biopsy” likely represents an unrecognized example of this entity [27]. It is possible that some of the cases of isolated glomerulomegaly represent unsampled O-FSGS because the mean number of glomeruli sampled in biopsies with O-GM was 6.4 (vs. 14.2 in O-FSGS). Nonetheless, the occurrence of O-GM in nearly 20% of our study group, despite an ample glomerular sampling in many cases, suggests that obesity-induced proteinuria results from adaptive structural-functional alterations causing glomerular hypertrophy and may not require the development of FSGS. Although it is possible that some of these cases will evolve into FSGS, no patient in this group developed renal insufficiency in the follow-up period. The importance of glomerulomegaly and renal hypertrophy in the pathophysiology of obesity-associated proteinuria is underscored by the higher kidney weights observed at autopsy in obese patients compared to non-obese controls [8].

In addition to focal segmental glomerulosclerosis and glomerulomegaly, 45% of ORG biopsies had focal glomerular basement membrane thickening or focal mesangial sclerosis reminiscent of the changes seen in early diabetic nephropathy (Fig. 2 D, E). Although seven of these patients were known to have NIDDM or glucose intolerance, they did not meet morphologic criteria for a diagnosis of diabetic nephropathy (that is, both diffuse mesangial sclerosis and glomerular basement membrane

thickening). These findings correlate with the observation that “occult” diabetic nephropathy is common in obesity [12] and may reflect the higher prevalence of glucose intolerance, hyperinsulinemia, and hyperlipidemia in the obese population.

The pathophysiology of obesity-induced glomerulomegaly and glomerular sclerosis is incompletely understood. Recent physiologic studies indicate that obese patients have elevations of both renal plasma flow and glomerular filtration rate (GFR) that exceed those of controls by 31% and 51%, respectively, leading to increased filtration fraction [7]. They postulate a role for afferent arteriolar dilation in the mediation of the increased transcapillary hydraulic pressure gradient. Elevation in GFR may be mediated in part by increased protein consumption. Because insulin directly reduces norepinephrine-induced efferent arteriolar constriction, insulin resistance could have the effect of increasing the transcapillary pressure gradient by increasing efferent arteriolar resistance [28]. Hyperinsulinemia has been shown to stimulate the synthesis of growth factors such as insulin-like growth factor (IGF)-1 and IGF-2, which may promote glomerular hypertrophy [29]. Elevated plasma levels of leptin in obesity [6] may predispose to glomerulosclerosis through up-regulation of transforming growth factor- β_1 (TGF- β_1) [30]. Hyperlipidemia itself also may promote glomerulosclerosis through mechanisms that involve engagement of low-density lipoproteins (LDL) receptors on mesangial cells, oxidative cellular injury, macrophage chemotaxis, and increased production of fibrogenic cytokines [31]. Recent evidence suggests that hyperlipidemia may also mediate FSGS by a direct podocyte toxicity [32].

The combination of focal segmental glomerulosclerosis and glomerulomegaly in ORG resembles the secondary forms of focal segmental glomerulosclerosis arising in conditions of chronic hypoxia and altered glomerular capillary hemodynamics, such as cyanotic congenital heart disease, sickle cell nephropathy, polycythemia and idiopathic pulmonary hypertension [33–35]. In all these conditions, FSGS develops despite an initially normal nephron number. Similarly, hypoxia, hypercapnia and systemic venous hypertension have been reported in obesity-induced sleep apnea [36, 37]. Even disordered sleep breathing, in the absence of overt sleep apnea, can cause hypoxia-mediated activation of sympathetic nervous system, as evidenced by microneurographic studies and catecholamine levels [38, 39]. Sleep apnea may cause dysregulation of glomerular capillary hemodynamics directly through sympathetic control of efferent arteriolar tone and indirectly through sympathetic activation of the renin-angiotensin system (RAS). There is some evidence that hyperinsulinemia itself can also activate the RAS [40, 41]. Finally, data from experimental animals suggest that obesity promotes increased ma-

trix deposition in the medullary interstitium (abstract; Arnold et al, *Lab Invest* 70:156, 1994) [42] and that the secondary effects on tubular sodium handling may stimulate the RAS [43, 44]. To this point, it is of interest that 20% of ORG patients had histologic evidence of JGA hyperplasia, of whom half had no history of systemic hypertension.

The first line of therapy in ORG should be correction of the underlying condition. Although difficult to achieve, weight loss alone can reduce proteinuria, as demonstrated in several of our patients and reported by others [30, 45]. Proteinuria has also been reported to respond to improved blood oxygenation following treatment of obstructive sleep apnea [46]. Lipid lowering agents, especially HMG-CoA reductase inhibitors, are effective in reducing mesangial sclerosis and proteinuria in obese Zucker rats [47], however their role in humans remains to be defined. ACE-I has been shown to be effective in reducing proteinuria in obese populations [24], a trend also observed in our cohort. Longer follow-up will be required to determine the potential benefits of prolonged ACE inhibition in allaying progression to end-stage renal disease and preventing the possible evolution of O-GM to O-FSGS. Four patients in our study were treated with steroids because one or more of the clinicopathologic features (abrupt onset of nephrotic-range proteinuria, severe nephrotic syndrome, cellular features of FSGS, or marked foot process effacement at biopsy) suggested the possibility of idiopathic FSGS. Indeed, the response to steroids observed in two of these cases suggests that not all obese patients with FSGS necessarily manifest ORG and that this population is not protected from the development of idiopathic FSGS.

In conclusion, ORG is an increasingly prevalent condition that develops in submorbid (class I and II) as well as morbid (class III) obesity. It typically manifests with nephrotic range proteinuria, but lacks nephrotic syndrome. Clinically, it is distinguished from I-FSGS by its lower incidence of nephrotic syndrome, more benign course, and slower progression to renal failure. Morphologic features include the consistent presence of glomerulomegaly, predominance of classic perihilar lesions of sclerosis, and relatively mild foot process fusion. However, because there is significant overlap in clinical and pathologic features with idiopathic FSGS, heightened physician awareness of this entity is required to insure accurate diagnosis and appropriate therapy.

Reprint requests to Vivette D. D'Agati, M.D., Department of Pathology, Columbia University, College of Physicians and Surgeons, 630 West 168th St., New York, New York 10032, USA.
E-mail: vdd1@columbia.edu

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