Obesity-Related Glomerulopathy in China: A Case Series of 90 Patients

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Background: The epidemic of obesity has been paralleled by an increase in the incidence of chronic kidney disease. However, epidemiological data for obesity-related glomerulopathy (ORG) from developing countries, including China, are very limited.

Study Design: Case series. ORG defined as body mass index (BMI) of 28.0 kg/m^2 or greater; urinary protein excretion of 0.4 g/24 h or greater, and glomerulomegaly (glomerular volume $> 3.27 \times 10^6$ μm^3) with or without focal segmental glomerulosclerosis (FSGS).

Setting & Participants: 10,093 renal biopsy samples from patients obtained from February 2002 to November 2006 at the Research Institute of Nephrology, Nanjing University School of Medicine, China.

Predictor: Obesity defined as a BMI of 28.0 kg/m^2 or greater. Subjects were divided into 3 groups: mild-obesity group with BMI of 28.0 to less than 30 kg/m^2, moderate-obesity group with BMI of 30 to less than 35 kg/m^2, and severe-obesity group with BMI of 35 kg/m^2 or greater.

Outcomes & Measurements: Clinicoepidemiological and histopathologic characteristics of patients with ORG at the time of biopsy were described separately.

Results: ORG was observed in 90 biopsy specimens (0.89%); frequency increased from 0.62% to 1.0% during the last 5 years ($P = 0.02$). Mean age was 37.5 $\pm$ 9.3 (SD) years, 67% were men, mean BMI was 31.2 $\pm$ 3.3 kg/m^2, waist circumference was 103 cm (range, 89.4 to 124 cm) in men and 96.5 cm (range, 88.5 to 113 cm) in women, waist-hip ratio was 0.95 $\pm$ 0.07, and 100% had visceral obesity. Of the total, 49%, 37%, and 14% had mild, moderate, and severe obesity, respectively. Mean urinary protein excretion of subjects was 1.48 $\pm$ 1.2 g/24 h; 51%, 39%, and 10% had proteinuria with protein of 0.4 to 1.0, 1.0 to 3.5, and greater than 3.5 g/d, respectively. Mean measured creatinine clearance (Ccr) was 109 $\pm$ 32.2 mL/min/1.73 m^2, with 42%, 36%, and 22% with a Ccr greater than 120, 90 to 120, and less than 90 mL/min/1.73 m^2, respectively. Glucose dysmetabolism, insulin resistance, dyslipidemia, and hypertension were observed in 77%, 88%, 76%, and 63% of patients, respectively. FSGS was observed in 70%. Mean foot-process width was 534 $\pm$ 176 nm. Foot-process fusion was seen in 36% of patients. Greater BMI was associated with greater proteinuria ($P < 0.02$), greater Ccr ($P < 0.03$), and greater foot-process width ($P < 0.04$).

Limitations: Inability to compute prevalence or incidence from case series. BMI was calculated at time of renal biopsy.

Conclusions: Most patients with ORG had mild obesity, visceral obesity, minor proteinuria, preserved Ccr, and FSGS.

Am J Kidney Dis 52:58-65.

INDEX WORDS: Obesity-related glomerulopathy; Chinese population; epidemiology study; obesity.

The emerging epidemic of obesity has threatened the health of millions of people worldwide.[1] Obese individuals are at greater risk of developing diabetes mellitus, hyperlipidemia, hypertension, and vascular diseases.[2] Recently, obesity was reported to be associated strongly with the development and progression of chronic kidney disease, a widely prevalent but often silent condition manifesting mostly in the form of proteinuria and glomerular injury with a distinctive clinicopathologic feature; obesity-related glomerulopathy (ORG).[3,4]

The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program, based on data collected in a white population, defined obesity as body mass index (BMI) of 30 kg/m^2 or greater.[5] However, using this criterion, Asians often are considered nonobese populations. Thus, the Working Group on Obesity in the Mainland of China redefined obesity by decreasing the cutoff level for BMI to 28 kg/m^2 in a Chinese cohort.[6] Increased risks associated with obesity were shown to occur at low BMIs in Asians,

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Received October 15, 2007. Accepted in revised form February 19, 2008. Originally published online as doi: 10.1053/j.ajkd.2008.02.303 on April 16, 2008.

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0272-6386/08/5201-0009$34.00/0
doi:10.1053/j.ajkd.2008.02.303

partly because these populations are predisposed to visceral obesity. In ATP III, visceral obesity was defined as a waist circumference greater than 102 cm in men or greater than 88 cm in women, respectively. Those values were adjusted to greater than 85 cm and greater than 80 cm for Chinese men and women, respectively.[2,3]

In 2004, we first reported that cases of ORG were increasing in a Chinese cohort.[7] Since then, we noticed that the prevalence of ORG was steadily increasing with the epidemic of obesity, which agrees with published studies.[8] Therefore, retrospective clinicoepidemiological studies were performed to examine the histopathologic findings of ORG in a Chinese population. It is the largest series to date of patients with this disorder.

METHODS

Participants

All 10,093 renal biopsy specimens were reviewed retrospectively for evidence of ORG from a single unit (Research Institute of Nephrology, Nanjing University School of Medicine, PR China) from February 2002 to November 2006. In this institute, indications for renal biopsy included proteinuria and/or hematuria and/or renal insufficiency, with or without coexisting systemic disease.[8] Biopsies were performed by the same group of clinicians, and renal biopsy specimens were examined by experienced nephrologists after preparation. Analysis included light microscopy, immunohistology, and electron microscopy. A final diagnosis was made for each patient on the basis of both clinical and histological investigations. Informed signed consents were obtained for all patients, and this analysis was approved by local authorities.

The diagnosis of ORG was established by[9-11]: (1) obesity (BMI $\geq$ 28.0 kg/m^2), (2) positive proteinuria (urinary protein excretion $\geq$ 0.4 g/24 h), and (3) presentation with obesity-associated focal segmental glomerulosclerosis (FSGS) with glomerulomegaly or obesity-associated glomerulomegaly alone. Glomerulomegaly was defined as glomerular volume greater than 3.27×10^6 μm^3.[10] Idiopathic cases of FSGS and minimal change disease were carefully ruled out according to clinical and histological characteristics, including variants in glomerular size, diffuse foot-process effacement, and segmental glomerular scarring. Other underlying conditions that could cause FSGS or glomerulomegaly were excluded carefully, such as diabetic nephropathy and hypertensive nephrosclerosis.

Patient charts were reviewed for age, sex, and presenting clinical and physical data. BMI was calculated based on height and weight at the time of renal biopsy. Obesity was defined as BMI of 28.0 kg/m^2 or greater, and visceral obesity was defined as waist circumference greater than 85 cm in men or greater than 80 cm in women.[3] The following definitions were used[5,12]: nephrotic-range proteinuria, 24-hour urine protein excretion of 3.5 g or greater; minor proteinuria, 24-hour urine protein excretion less than 1 g; hypoalbuminemia, serum albumin level of 3.5 g/dL or less ($\leq$35 g/L); nephrotic syndrome, the combination of nephrotic-range proteinuria, hypoalbuminemia, and edema; hypertension, blood pressure of 140/90 mm Hg or greater or use of antihypertensive medication; glucose dysmetabolism, impaired fasting glucose level (fasting plasma glucose, 110 to 125 mg/dL [6.1 to 7.0 mmol/L]) or impaired glucose tolerance (2-hour plasma glucose after a standard 75-g glucose load, 140 to 199 mg/dL [7.8 to 11.1 mmol/L]); dyslipidemia, cholesterol level greater than 240 mg/dL (>6.2 mmol/L), triglyceride level greater than 200 mg/dL (>2.2 mmol/L), low-density lipoprotein cholesterol level greater than 120 mg/dL (>3.1 mmol/L), and/or high-density lipoprotein cholesterol level less than 40 mg/dL (<1.0 mmol/L).

Creatinine clearance (Ccr) was calculated by means of 24-hour urine collection using the standard formula: urine creatinine (mg/dL) $\times$ urine volume (mL/min)/serum creatinine (mg/dL) and adjusted for body surface area.[13] Glomerular hyperfiltration was defined as Ccr greater than 120 mL/min/1.73 m^2 (>2.0 mL/s/1.73 m^2), and renal insufficiency was defined as serum creatinine level greater than 1.24 mg/dL (>110 mmol/L) and/or Ccr less than 60 mL/min/1.73 m^2 (<1.00 mL/s/1.73 m^2).[12] Urinary *N*-acetyl-β-D-glucosaminidase (NAG) level was determined by using colorimetric measurement and expressed in units per gram of creatinine (U/g$_{cr}$), and retinol-binding protein (RBP) level was determined by means of enzyme-linked immunosorbent assay. Tubular injury was defined as NAG level greater than 16.5 U/g$_{cr}$ or RBP level greater than 0.5 mg/L. Plasma insulin was measured by means of radioimmunoassay. Homeostasis Model Assessment of Insulin Resistance was calculated by using the formula: fasting serum insulin (μU/mL) $\times$ fasting plasma glucose (mmol/L)/22.5, and insulin resistance was defined as a Homeostasis Model Assessment of Insulin Resistance greater than 2.18.[14] Visceral fat areas were measured by using computed tomography (Biograph Sensation 16, Siemens Medical Solutions, Erlangen, Germany) in a single tomographic slice at the L4 to L5 level, expressed in centimeters squared.[15]

Periodic acid–Schiff–stained paraffin-embedded light microscopy slides at original magnification $\times$400 were used to estimate mean glomerular volume by using the method of Weibel and Gomez. Mean glomerular volume [V(glom)] was calculated as[16]: $V(glom) = 0.75 \times [\Sigma Pg \times (d/mag)^2]^{3/2} + 0.21$, where ΣPg is number of points hitting the glomerular profile, d is the distance between coarse grid points, mag is magnification, and 0.75 and 0.21 are both factors from line regression. The correction factor of 2.09 is used for conversion to allow comparisons with previous published studies.[17] An average of 50 glomerular sections were examined by light microscopy and categorized as global or segmental glomerulosclerosis. A set of electron micrographs of images obtained at an original magnification of $\times$20,000 was used for measurements. Podocyte foot-process width on peripheral glomerular basement membrane (GBM) or filtration surface was measured[18]: $FPW = (\pi/4) \times (\Sigma GBM\ length/\Sigma foot\ process)$, where ΣGBM length is total length of peripheral GBM in each picture, Σfoot process is total number of foot processes on peripheral GBM, and the