Reversible Glomerular Hypertrophy in Adult Patients with Primary Focal Segmental Glomerulosclerosis

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Abstract. The present study was performed to assess the pathogenetic role of glomerular hypertrophy in patients with primary focal segmental glomerulosclerosis (FSGS). We studied 14 patients with FSGS by morphometry. In seven patients, minimal change nephrotic syndrome (MCNS) was diagnosed on the first renal biopsy, but FSGS was diagnosed on the second biopsy (MCNS-FSGS group). Seven other patients with FSGS on the first biopsy underwent second biopsies while in remission (FSGS-R group). Biopsy results were compared with biopsies from 10 patients with MCNS and seven control subjects. Nonsclerotic glomeruli were examined. The mean glomerular tuft area, whole glomerular area, and number of mesangial cells were significantly increased in both biopsies from the MCNS-FSGS group and in the first biopsies obtained during the nephrotic stage of the FSGS-R group, compared with control subjects and patients with MCNS. Biopsies from FSGS patients in remission showed that the mean glomerular tuft area and number of mesangial cells were significantly decreased. The fractional extracellular matrix area (extracellular matrix area/glomerular tuft area) and mesangial cell density (mesangial cell number/glomerular tuft area) in FSGS during both nephrotic and remission stages were the same as those in control subjects and patients with MCNS. The present study suggests that glomerular hypertrophy precedes the development of glomerulosclerosis in FSGS and is reversible when patients are in remission. These features support the pathogenetic importance of glomerular hypertrophy in patients with primary FSGS. (J Am Soc Nephrol 8: 1668–1678, 1997)

Glomerular hypertrophy plays a crucial role in the pathogenesis of segmental sclerotic lesions, as demonstrated by renal ablation studies showing an association between glomerular hypertrophy and progressive glomerular sclerosis in rats (1–3). Segmental sclerotic lesions can be found in a variety of human renal diseases, and glomerular hypertrophy with segmental sclerosis has been identified in reflux nephropathy (4,5) and kidneys with reduced functional mass (6,7). However, it remains unknown whether such an association occurs in patients with primary focal segmental glomerulosclerosis (FSGS) who present with nephrotic syndrome. To address this, several studies focusing on glomerular hypertrophy in children and adults with FSGS have been performed (8–12). Consistent findings from these studies demonstrate that glomerular size in patients with FSGS is significantly greater than that of patients with minimal change nephrotic syndrome (MCNS). Furthermore, Fogo et al. (8) have suggested that glomerular hypertrophy in children with MCNS may be an indicator for a high risk of progression to FSGS. Nyberg et al. (10) and our previous study (13) demonstrated that glomerular size is a useful predictor of steroid response or renal outcome.

If glomerular hypertrophy is closely associated with the development of FSGS, glomerular size should be reversible and return to normal after a remission is obtained. To elucidate this hypothesis, we examined nonsclerotic glomeruli of 14 adult patients with FSGS who underwent repeat renal biopsy; seven patients were in remission when the second biopsy was performed.

Materials and Methods

Patients

Thirty-seven adult Japanese patients with primary FSGS and nephrotic syndrome seen between 1980 and 1995 formed the patient population for this study. We studied 14 patients with FSGS who underwent repeat renal biopsies and whose specimens included a sufficient number of glomeruli. They were divided into two groups according to their clinical status and morphological diagnosis at the time of biopsy; seven patients had an initial diagnosis of MCNS by renal biopsy and a second biopsy showing progression to FSGS (abbreviated as MCNS-FSGS). Seven other patients had an initial diagnosis of FSGS by renal biopsy performed during the nephrotic phase and underwent a second biopsy during complete or incomplete (partial) remission (abbreviated as FSGS-R). Clinical data for control subjects and for patients with FSGS and MCNS are shown in Table 1. The MCNS-FSGS group consisted of three men and four women, who ranged in age at onset from 15 to 59 yr (average, 40 yr). Five patients showed persistent, steroid-resistant nephrotic syndrome. The remaining two had an incomplete remission with normal creatinine clearance after steroid therapy and exhibited FSGS during a relapse of nephrotic syndrome. Interval from first to second biopsy ranged from 7 to 56 mo (average, 20.9 mo). The FSGS-R group included five men and two women ages 21 to 65 yr (average, 30.8 yr). At the time of second biopsy, four patients were in complete remission and three patients were in incomplete (partial) remission. Interval from first to second biopsy ranged from 3 to 54 mo (average, 24.3 mo). We also examined...
10 patients with steroid-sensitive MCNS who underwent a complete remission. The MCNS group consisted of five men and five women, and their age at onset varied from 19 to 60 yr (average, 32.9 yr). All patients in the MCNS-FSGS, FSGS-R, and MCNS groups underwent renal biopsy within 1 mo of disease onset. In the control group, renal tissues were obtained from normal-appearing portions of kidneys that were removed from seven patients with renal cell carcinoma or renal cyst. There were five men and two women who ranged in age from 46 to 73 yr (average, 58.7 yr).

Complete remission was defined as urine free of protein, normal serum albumin, and normal renal function for at least 1 mo. Incomplete (partial) remission was defined as the disappearance of nephrotic syndrome and normal renal function, but persistence of mild proteinuria (less than 1.0 g/d).

Pathology
All patients gave informed consent. Tissue obtained from percutaneous renal biopsy was divided into three parts for light microscopy, immunofluorescence studies, and electron microscopy. Tissue for light microscopy was fixed in 10% buffered formalin and embedded in paraffin. Routinely, eight to 10 sections were prepared and were stained with hematoxylin and eosin, periodic acid-Schiff (PAS), periodic acid-silver methenamine, and Masson's trichrome. In addition, 30 to 50 serial sections stained with PAS were used in all four groups. All biopsy specimens were examined without knowledge of the clinical outcome.

Using the routinely prepared sections and serial sections, we counted total number of glomeruli included and glomeruli with segmental or global sclerosis, obtained maximal cross-sectional area of glomerulus, and evaluated the area of segmental sclerosis and severity of tubulointerstitial changes and vascular lesions. The prevalence of segmental sclerosis and global sclerosis was expressed by fraction of total glomeruli included. The maximal cross-section of glomerulus was used in morphometrical analysis. The first biopsy specimens of the MCNS-FSGS and FSGS-R groups contained 15.9 ± 5.7 (8 to 23) and 31.4 ± 11.8 (17 to 51) glomeruli, respectively. The second biopsies of the MCNS-FSGS and FSGS-R groups possessed 19.0 ± 6.0 (14 to 32) and 39.1 ± 23.7 (12 to 71) glomeruli, respectively. The biopsy specimens of the MCNS group included 37.0 ± 12.4 (23 to 62) glomeruli.

Tubulointerstitial changes consisted of tubular atrophy, interstitial fibrosis, and mononuclear cell infiltration. The extent of tubulointerstitial changes was assessed semiquantitatively: 0, absent; 1+, lesions occupying less than 20% of renal cortex in the biopsy specimen; 2+, more than 20% of renal cortex affected. In each patient, we recorded the grade of tubulointerstitial lesions in every other 5 to 10 sections, added the points of each specimen, and calculated a mean score. The presence of vascular lesions was defined as the presence of hyalinosis in the arteriolar walls or intimal thickening in the interlobular arteries within all specimens, or both.

Morphometric Analysis
An SPICCA II image analysis processor (Olympus, Japan) was used for estimation of the glomerular size. In comparison with the glomerular size in each group, glomeruli that had a sclerotic lesion were excluded from analysis. There were no glomeruli showing a glomerular cystic lesion. We randomly selected glomeruli and obtained their maximal cross-sectional area, using serial sections. The number of glomeruli we examined was as follows: 9.5 ± 1.6 and 10.6 ± 0.8 in the first and second biopsy specimens of the MCNS-FSGS group, respectively; 10.6 ± 1.1 and 10.7 ± 0.8 in the first and second biopsy specimens of the FSGS-R group, respectively; 10.3 ± 0.9 in the MCNS group; and 10.0 ± 0.0 in the control group.

The glomerular tuft area (GTA), extracellular matrix area (EMA), mesangial cells, and whole glomerular area (WGA) were quantitatively analyzed according to the previous report (14). Microscopic images of the maximal cross-sectional area of glomerulus stained with PAS were projected using a ×40 objective lens at a final magnification of ×400 and put into the SPICCA II system through the video camera. The outlines of the glomerular tuft were identified and encircled manually. The image of the encircled area (GTA) was measured by the SPICCA II system. The WGA defined by the internal edge of the Bowman's capsule was measured. The EMA of the maximal cross-sectional area was automatically identified according to color density differences, particularly careful not to overestimate or underestimate EMA. The fractional EMA was expressed as EMA per GTA. The number of mesangial cell nuclei (MN) in the maximal cross-sectional area was also counted. The fractional MN were defined as the number of MN per GTA × 100.

The severity of segmental sclerosis was also examined quantitatively. The segmental sclerotic lesion was manually encircled and measured automatically by the SPICCA II system. The area of glomerular sclerosis was expressed as total area of sclerosis per total GTA of glomeruli included. We examined every other 5 to 10 sections, six sections in all. The areas of each specimen were added, and a mean area was calculated.

Statistical Analyses
Comparison between the four groups was performed with a one-way ANOVA followed by Scheffé's test. Results of the serial biopsies were analyzed by Wilcoxon matched-pairs signed-rank test. The relation between glomerular size and the other morphological parameters was obtained by least-squares linear regression analysis or Spearman's rank correlation. Statistical significance was considered achieved if P < 0.05. Results are given as mean ± SD.

Results
Clinical Characteristics
Clinical features in control subjects and in patients with FSGS and MCNS are shown in Table 1. The mean age at onset was greater in the MCNS-FSGS group than in the FSGS-R group and MCNS group, but it was not significant. The interval period from initial to second biopsy was not different between MCNS-FSGS and FSGS-R groups. On the first biopsy, the mean serum creatinine concentration in MCNS-FSGS and FSGS-R groups was significantly greater than that in the MCNS group. In addition, the mean creatinine clearance in the MCNS group was significantly higher than in the MCNS-FSGS group. At the time of the second biopsy, the mean serum creatinine concentration in the MCNS-FSGS group was significantly elevated, and the creatinine clearance decreased compared with the FSGS-R group.

All patients with FSGS and MCNS received prednisolone therapy, with an initial dosage of 40 to 60 mg/d, perorally. Five patients in the MCNS-FSGS group and five in the FSGS-R group were treated with 50 to 100 mg/d of cyclophosphamide perorally for 4 to 8 wk or 3 mg/kg cyclosporin A perorally for 6 mo, or both. Although patients in the control group were the oldest among the four groups, their renal function was normal. We therefore included this group in further examinations.
Table 1. Clinical data in control subjects and in patients with FSGS and MCNS

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Cases</th>
<th>Age (yr)</th>
<th>Sex (M/F)</th>
<th>Interval to Second BX (mo)</th>
<th>First BX</th>
<th>Second BX</th>
<th>First BX</th>
<th>Second BX</th>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Proteinuria (g/d)</td>
<td>S cr (mg/dl)</td>
<td>C cr (ml/min)</td>
<td>Proteinuria (g/d)</td>
</tr>
<tr>
<td>MCNS-FSGS</td>
<td>7</td>
<td>40.0 ± 17.0</td>
<td>3/4</td>
<td>(3 to 54)</td>
<td>14.4 ± 9.2</td>
<td>1.4 ± 0.3</td>
<td>57.1 ± 19.0</td>
<td>20.6 ± 10.0</td>
</tr>
<tr>
<td>FSGS-R</td>
<td>7</td>
<td>30.8 ± 15.8</td>
<td>5/2</td>
<td>(7 to 56)</td>
<td>10.2 ± 3.0</td>
<td>1.4 ± 0.5</td>
<td>70.0 ± 11.5</td>
<td>0.3 ± 0.3</td>
</tr>
<tr>
<td>MCNS</td>
<td>10</td>
<td>32.9 ± 12.5</td>
<td>5/5</td>
<td>NA</td>
<td>13.7 ± 9.3</td>
<td>0.9 ± 0.3</td>
<td>86.0 ± 20.5</td>
<td>NA</td>
</tr>
<tr>
<td>Control</td>
<td>7</td>
<td>58.7 ± 10.9</td>
<td>5/2</td>
<td>NA</td>
<td>0.0</td>
<td>0.8 ± 0.1</td>
<td>90.6 ± 17.1</td>
<td>NA</td>
</tr>
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</table>

* FSGS, primary focal segmental glomerulosclerosis; MCNS, minimal change nephrotic syndrome; BX, biopsy; S cr, serum creatinine concentration; C cr, endogenous creatinine clearance; FSGS-R, remission stage of FSGS; NA, not applicable.

Pathology

The glomeruli in the MCNS group showed no remarkable changes. However, one patient exhibited small foci of tubular atrophy and interstitial fibrosis in the serial sections. A comparison between the first and second biopsy findings of patients with FSGS was made (Tables 2 and 3). The first and second biopsies in patients with FSGS showed only minimal to mild mesangial alteration apart from sclerosis. None of our patients showed mesangial cell proliferation, defined as more than three mesangial cells per peripheral mesangial area. In the MCNS-FSGS group, the first biopsies showed hypertrophied glomeruli. Tubulointerstitial changes, corresponding to grade 1, and vascular lesions were observed in three and two patients, respectively. Three patients showed hyalinized glomeruli. Electron microscopy revealed diffuse effacement of foot processes. In the second biopsies, glomeruli were hypertrophic. The prevalence of IgM deposition in the mesangial area was significantly increased in the second biopsy than in the first biopsy. In an electron microscopic observation of the second biopsies, vacuolation and local detachment of the epithelial cells were added to effacement of foot processes (Table 2). Tubulointerstitial lesions significantly worsened during the progression of FSGS (Table 3).

In the FSGS-R group, the first biopsies showed hypertrophied glomeruli with segmental sclerosis. Tubulointerstitial and vascular lesions were observed in three and two patients, respectively. In the second biopsy, segmental sclerotic lesions occasionally associated with hyalinosis were invariably observed. Glomeruli obtained in the second biopsy (during remission) were apparently smaller than glomeruli in the first biopsy (during nephrotic syndrome) (Figure 1). The prevalences of IgM deposition and vascular lesion did not change in the FSGS-R group. Electron microscopy demonstrated remarkable improvement of the epithelial cell damage except for local

Table 2. Pathological characteristics in the MCNS-FSGS and FSGS-R groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Location of FSGS Lesion</th>
<th>Prevalence of Vascular Lesion</th>
<th>Prevalence of IgM Deposition</th>
<th>Electron Microscopic Findings of the Epithelial Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First BX</td>
<td>Second BX</td>
<td>First BX</td>
<td>Second BX</td>
</tr>
<tr>
<td>MCNS-FSGS</td>
<td>None</td>
<td>Hilar; 5 cases</td>
<td>2 of 7</td>
<td>3 of 7</td>
</tr>
<tr>
<td></td>
<td>Peripheral; 2 cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSGS-R</td>
<td>Peripheral; 2 cases</td>
<td>Tip; 2 cases</td>
<td>2 of 7</td>
<td>3 of 7</td>
</tr>
<tr>
<td></td>
<td>Tip; 1 case</td>
<td></td>
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</table>

* Hilar type, segmental sclerosis present in the hilar region of glomerulus; peripheral type, segmental sclerosis limited in the peripheral tuft of glomerulus; tip lesion, sclerosis is located in the vicinity of the tubular pole comprised of foam cells and an adhesion.
loss of foot processes. The prevalence and area of glomerular sclerosis, and the severity of tubulointerstitial lesion in the first biopsy specimens were not different from those in the second biopsy specimens. Compared with the second biopsy specimens, the area of glomerular sclerosis and the severity of tubulointerstitial lesions in the MCNS-FSGS group were significantly greater than those in the FSGS-R group.

**Morphometry**

In the first biopsies, the mean GTA in the MCNS-FSGS group was similar to that in the FSGS-R group. The mean GTA in the MCNS-FSGS and FSGS-R groups were significantly greater than those in the MCNS and control groups and were 1.3 to 1.4 times as large (Figure 2). The mean WGA in the MCNS-FSGS group was significantly greater than that in the MCNS and control groups. The mean WGA in the FSGS-R group was significantly greater than that in the MCNS group, but was not significantly different compared with the control groups. The mean EMA in the MCNS-FSGS, FSGS-R, and MCNS groups were greater than that in the control groups, but it was not significant. Although the fractional EMA (EMA/GTA) in the MCNS group was the greatest among four groups, no significant differences were evident. The number of mesangial cells in the MCNS-FSGS group remained significantly greater than that in the FSGS-R group and other morphological parameters was analyzed. GTA did not correlate with the prevalence of segmental sclerosis, area of segmental sclerosis, or grade of tubulointerstitial lesion (r = 0.164, P = 0.83, r = 0.199, P = 0.50, r = 0.441, P = 0.12, respectively).

**Discussion**

Several morphometric studies have been performed in children and adults with FSGS (8–12). However, to our knowledge, there is no quantitative report of the changes in glomerular size between the nephrotic stage and remission stage of FSGS. The present study demonstrates that GTA, WGA, and EMA in adult patients with FSGS were significantly greater than those in control subjects and adult patients with MCNS. Our observations are in agreement with those of previous studies performed in children and adults that show kidneys with FSGS are characterized by larger glomeruli compared with kidneys from patients with MCNS or from normal individuals (8–12).

The biopsy specimens obtained during remission demonstrated that the glomerular hypertrophy present during nephrotic stage disappeared completely. In general, FSGS patients in remission show a favorable outcome; however, 60 to 70% of FSGS patients resistant to treatment develop end-stage renal disease after 5 to 10 yr (15). Taken together, these results suggest that the glomerular hypertrophy is associated with the progression of patients with primary FSGS.

There is controversy as to whether glomerular hypertrophy plays a pathogenetic role in the development of FSGS or whether it is merely a morphological finding. This controversy appears to stem from differences in the doctrine concerning MCNS and FSGS; some authors consider MCNS and FSGS to be different diseases, whereas others suggest that they represent a spectrum of presentations of the same disease process (8,16,17). Evidence for an occurrence of transition from MCNS to FSGS in animals has recently been established in experimental models of Adriamycin nephropathy and aminonucleoside nephropathy (18,19). Fogo et al. (8) reported that the initial biopsy of pediatric patients with MCNS who subsequently developed FSGS had a larger GTA than glomeruli from patients with MCNS and suggested that glomerular hypertrophy precedes the development of glomerulosclerosis. The study presented here also demonstrated that in the MCNS-FSGS group the first biopsy without sclerotic lesions had larger glomeruli than those in control subjects and patients with MCNS. Conversely, Lee and Lim (12) recently mentioned that

<table>
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<tr>
<th>Group</th>
<th>Prevalence of Segmental Sclerosis</th>
<th>Prevalence of Global Sclerosis</th>
<th>Area of Segmental Sclerosis</th>
<th>Grade of Tubulointerstitial Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First BX</td>
<td>Second BX</td>
<td>First BX</td>
<td>Second BX</td>
</tr>
<tr>
<td>MCNS-FSGS</td>
<td>0</td>
<td>21.68 ± 12.69</td>
<td>6.22 ± 7.95</td>
<td>10.36 ± 12.72</td>
</tr>
<tr>
<td>FSGS-R</td>
<td>16.86 ± 12.90</td>
<td>15.45 ± 13.23</td>
<td>2.98 ± 6.78</td>
<td>4.61 ± 3.83</td>
</tr>
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</table>

* P < 0.05.
Figure 1. Representative features of glomeruli in minimal change nephrotic syndrome (MCNS) and primary focal segmental glomerulosclerosis (FSGS). The glomeruli obtained in nephrotic FSGS (middle) are much larger than glomeruli from MCNS (top). In remission, glomeruli obtained from the same patient (bottom) return to normal size. Arrow indicates small area of hyalinosis (periodic-acid Schiff staining; magnification, ×138).

glomerular hypertrophy tends to coexist with FSGS. Their opinion is based mainly on findings that the mean glomerular volume significantly correlated with percentage of glomerulosclerosis, which in turn correlated with affected interstitial volume, as well as mesangial volume. In contrast to their findings, the present study showed that glomerular size did not correlate with the severity and percentage of glomerulosclerosis or severity of tubulointerstitial lesions. In all patients in the MCNS-FSGS and FSGS-R groups, renal biopsy was performed within 1 mo of the onset of disease. Furthermore, the enlarged glomerular size seen during nephrotic phase returned to normal after remission. A comparison of the second biopsies with the first biopsies in the FSGS-R group revealed that the percentage and area of glomerulosclerosis and severity of tubulointerstitial lesions did not change or were slightly worse. These findings suggested that glomerular hypertrophy in the early stage of FSGS may be associated with development of sclerotic lesions rather than occurring as compensatory phenomena. It is reasonable that an advanced stage of FSGS leads to compensatory glomerular hypertrophy.

Tubulointerstitial lesions and decreased renal function were observed on the first biopsy of the MCNS-FSGS group, which were similar to those on the first biopsy of the FSGS-R group. Although the presence of tubulointerstitial scarring leads nephrologists to search carefully for FSGS, mild changes have been reported in patients with MCNS (20,21), as the MCNS group showed. In the first biopsies of the MCNS-FSGS group, no characteristic findings of electron microscopy, such as detachment and vacuolation of the epithelial cells, were evident (22,23). Furthermore, the FSGS-R group invariably showed segmental sclerosis in the second biopsies, suggesting that absence of glomerulosclerosis in the first biopsies of the MCNS-FSGS group is unlikely to be merely a result of biopsy sampling (8). Although we cannot exclude the possibility that in the first biopsies of the MCNS-FSGS group segmental sclerosis is unrecognized, we agree with the opinion of Fogo et al. (8) that there is a unique subset of patients with MCNS who develop FSGS and exhibit glomerular hypertrophy. On the first biopsy of MCNS-FSGS and FSGS-R groups, renal function was significantly reduced compared with the MCNS group. Two patients in the MCNS-FSGS group and all in the FSGS-R group had normal renal function after treatment. Therefore, some patients of this unique subset may present with a reversible decline of renal function, as patients with FSGS do. Although the mechanism of renal dysfunction is unknown, a reduced creatinine clearance rate may be derived from microhemodynamic abnormalities.

Mesangial proliferation that includes an increase in cell number and matrix is one of the characteristic features of FSGS and is occasionally prominent in children (11,21). In our cases, the expansion of EMA was observed in the nephrotic stage of FSGS, but the fractional EMA was not significantly different among four groups. This contrasts with the findings of Suzuki et al. (11) and Lee and Lim (12), who have reported that the fractional EMA or mesangial volume in FSGS was significantly greater than those in MCNS. The reason for the difference between these results remains unclear, but may be due to differences in age and the time period that the biopsies were performed. With regard to cellular proliferation, our results concur because the density of mesangial cells did not differ. These findings suggest that in our cases the increase in EMA and cell number was proportional to overall glomerular hypertrophy.

It is now thought that the glomerular hypertrophy and seg-
Morphometric analysis of the first biopsies. Comparison between the control, MCNS, MCNS-FSGS, and remission stage of FSGS (FSGS-R) groups. The glomerular tuft area (GTA), whole glomerular area (WGA), and mesangial cell number (MN) of the MCNS-FSGS and FSGS-R groups are greater than those of the MCNS and control groups. \( *P < 0.05; \) \( **P < 0.01 \). EMA, extracellular matrix area.

Mental sclerosis are pathophysiologically linked. The glomerular hypertrophy leads to an increase in glomerular capillary luminal diameters, which may provoke mechanical injury of the glomerular epithelial cells (24,25). The epithelial cells are stretched and attenuated to cover the enlarged glomerular tuft, conceivably resulting in detachment from the glomerular basement membrane that is the hallmark of segmental sclerosis (22,25). However, the mechanism of the development of glo-
Figure 3. Morphometric analysis of the second biopsies. Comparison between the control, MCNS, MCNS-FSGS, and FSGS-R groups. The GTA, WGA, and EMA of the MCNS-FSGS group are greater than those of the FSGS-R, MCNS, and control groups. Glomerular size and mesangial cells of the FSGS-R group are similar to those of the MCNS and control groups. *P < 0.05; **P < 0.01.

glomerular hypertrophy is poorly understood. Many experimental studies, using partial nephrectomy model, have shown that physical loss of nephrons is required to trigger glomerular hypertrophy and glomerulosclerosis (1–3). Similar pathophysiological settings have been demonstrated in patients with nephrectomy (7), reflux nephropathy (4,5), and oligomeganephronia (26). However, this mechanism is unlikely to occur as an initiating event in primary FSGS. In recent studies, a
variety of cytokines and vasoactive substances have been shown to promote mesangial cell growth and stimulate mesangial matrix release \textit{in vitro}. Growth hormone (27), transforming growth factor-β1 (28-30), and angiotensin II (31) are thought to play an important role in the production of extracellular matrix by both animal and human mesangial cells. Regression
of glomerular hypertrophy means that the above-mentioned substances are completely and effectively suppressed by steroid, immunosuppressive drugs, angiotensin-converting enzyme inhibitors, or both. Because most patients with FSGS do not undergo remission regardless of various treatments, other factors that are resistant to these drugs remain to be identified.

Figure 5. Comparison of the first and second biopsies in the FSGS-R group. The GTA, WGA, and MN in the second biopsies are significantly smaller than those in the first biopsies ($P < 0.05$).
Regression of glomerular hypertrophy during remission is of particular interest. During the nephrotic phase of FSGS, an absolute increase in the number of mesangial cells, as well as an increase in mesangial matrix, was observed. Recently, one manner of cell death defined as apoptosis has been recognized in experimental and human glomerulonephritis (32–34). It is therefore likely that apoptosis may participate in the deletion of increased mesangial cells. Although apoptotic bodies are rarely observed in FSGS, such scarceness may be due to rapid clearance of apoptotic cells by phagocytosis (35). Extracellular matrix in the glomeruli is thought to be degraded by proteinases such as aspartic acid, cysteine, serine, and metalloproteinases under the regulation of tissue inhibitors and cytokines (36,37). It is assumed that the increase in extracellular matrix in non sclerotic glomeruli is reversible through the action of these proteinases.

In conclusion, the study presented here demonstrates that the glomerular hypertrophy present during the nephrotic stage of FSGS is reversible during remission, and provides additional support that the glomerular hypertrophy plays an important role in the development of sclerosis in patients with primary FSGS.

Acknowledgment
We are grateful to Mrs. M. Sakaida for her technical assistance.

References