Clinical features and long-term outcome of obesity-associated focal segmental glomerulosclerosis

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Abstract

Background. Several cases of obesity-associated focal segmental glomerulosclerosis (OB-FSG) have been reported but little is known about the clinicopathological features of this entity and its long-term outcomes.

Methods. We studied 15 obese patients (BMI 35 ± 5.2 kg/m²) with biopsy-proven FSG. They were compared with a control group of 15 non-obese patients with idiopathic FSG (I-FSG).

Results. Mean proteinuria at the time of renal biopsy was 3.1 ± 2 g/24 h in OB-FSG; it reached the nephrotic range (>3.5 g/24 h) during follow-up in 12 patients (80%), but none of them had oedema, hypoalbuminaemia, or hypoalbuminaemia. Proteinuria was increased most marked amongst I-FSG (6.5 ± 4.2 g/24 h) and most of them developed oedema and biochemical nephrotic syndrome. Glomerulomegaly was observed in all renal biopsies from OB-FSG patients (mean glomerular diameter 256 ± 24 μm in OB-FSG vs 199 ± 26 μm in I-FSG, P<0.001). Twelve OB-FSG patients (80%) were treated with ACE inhibitors (ACEI) and proteinuria significantly decreased within the first 6 months of treatment but showed a later increase. None of the obese patients achieved a sustained weight loss. Seven (46%) patients with OB-FSG experienced a progressive renal insufficiency and five of them started intermittent dialysis. Kaplan–Meier estimated probabilities of renal survival after 5 and 10 years were 77 and 51%, respectively, in OB-FSG patients, and 52 and 30% in I-FSG (P<0.05). The risk of developing progressive renal failure among OB-FSG patients was statistically correlated with serum creatinine and creatinine clearance at presentation.

Conclusions. OB-FSG indicates a poor prognosis with almost one-half of patients developing advanced renal failure. Knowledge of the clinicopathological features of this entity (obesity, FSG lesions with glomerulomegaly, absence of nephrotic syndrome despite nephrotic-range proteinuria) should be helpful in establishing an accurate and early diagnosis.

Keywords: ACE inhibitors; focal and segmental glomerulosclerosis; obesity; progression of renal insufficiency

Introduction

The presence of severe proteinuria as a complication of massive obesity was reported for the first time in 1974 [1]. Since then, a number of case reports and autopsy studies have described the morphologic characteristics of this renal complication [2–11] with the most common lesion being focal and segmental glomerulosclerosis (FSG). However, in some cases, only enlarged glomeruli or even normal renal biopsies were reported in obese patients with proteinuria [2,4,10,11]. From a clinical point of view, proteinuria found frequently in the nephrotic range, is the most common presentation [2–11]. The majority of reported patients had normal renal function.

Given the limited number of published cases of obesity-related FSG (OB-FSG) and that a significant number of them derive from autopsy studies, little is known about the outcome of these patients. Information about the clinical features that may distinguish these cases from idiopathic FSG (I-FSG) is also scarce. In the present study, we observed 15 obese patients with biopsy-proven FSG during a lengthy follow-up (82 ± 57 months, range 36–204), and described their

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clinical, morphologic, and prognostic characteristics in comparison with a control group of 15 non-obese patients with I-FSG.

Methods

We retrospectively studied 15 patients diagnosed with OB-FSG. The diagnosis was established by the presence of FSG lesions (segmental solidifications of the glomerular tuft in some glomeruli with immunofluorescence and electron microscopy findings compatible with the diagnosis of FSG) in obese patients. Obesity was defined as a body mass index (BMI) greater than 30 kg/m² (BMI calculated as the weight in kilograms divided by the square of height in meters). Class I obesity was defined as a BMI between 30 and 34.9, class II 35–39.9 and class III > 40 kg/m². Patients with diabetes mellitus, systemic disease, severe hepatic disorders, HIV, or those with FSG lesions superimposed upon other idiopathic or secondary glomerular diseases were excluded.

Clinical, analytic, and radiological features, both at the time of initial study and during follow-up, were obtained and analysed from case histories. The creatinine clearance was always adjusted for 1.73 m² of body surface area. The date of renal biopsy was considered to be the onset of follow-up. All the patients were visited every 3–6 months in our outpatient clinic. Physical examination, complete blood count, routine biochemical determinations, urine sediment examination, and a 24-h urine sample for measurement of creatinine clearance and daily proteinuria were obtained on each visit. Nephrotic proteinuria was defined as a 24-h proteinuria ≥3.5 g. Nephrotic syndrome was defined as a nephrotic-range proteinuria accompanied by hypoalbuminaemia (serum albumin <3 g/dl). Renal insufficiency was defined as a serum creatinine ≥1.4 mg/dl together with a creatinine clearance lower than 70 ml/min/1.73 m². Progressive renal insufficiency was indicated when serum creatinine increased ≥50% of baseline values during follow-up. Arterial hypertension was defined as systolic blood pressure greater than 140 mmHg and/or diastolic blood pressure greater than 90 mmHg. Mean arterial pressure (MAP) was calculated as the diastolic blood pressure plus one-third of the pulse pressure.

Renal biopsy specimens from the 15 patients were analysed for the percentage of normal, segmental, and global sclerotic glomeruli. The mean diameter of normal glomeruli was calculated in every biopsy. Measurements of glomerular diameter were performed using a micrometer mounted on an eye-piece (Leitz-Wetzlar), according to the manufacturer’s specifications. All glomeruli with four or more distinct capillary loops in a single stained PAS section were measured. Glomerular diameter was taken from the mean of two measures: the first was the distance between the peripheral basement membrane of the two more distant capillary loops and the second was the perpendicular diameter to the previous measurement. Glomerular diameter was measured in 3–15 glomeruli per patient and the mean of these values was the glomerular diameter for each patient. The severity of interstitial fibrosis, tubular atrophy, and arteriolosclerosis was graded semiquantitatively on a scale of 0–4, with 0 = none and 4 = severe.

Clinico-pathologic and laboratory data of OB-FSG patients were compared with those of non-obese 15 patients with I-FSG. The two groups were matched for renal function (serum creatinine and creatinine clearance at the time of renal biopsy). I-FSG was defined by the presence of FSG lesions in patients with normal renal morphology, by absence of vesicoureteral reflux, BMI < 30 kg/m², and no other discernible causes of FSG.

The statistical analysis of quantitative variables was performed using Wilcoxon tests and Mann-Whitney tests where appropriate. Qualitative variables were compared with Fisher’s exact tests. Pearson’s correlation coefficients were used to study the relationship between quantitative variables. Univariate logistic regression analysis was performed to identify predictors of renal insufficiency progression. Renal survival analysis was performed by the method of Kaplan and Meier, and statistical comparisons were made using the log rank test. Data are presented as means ± standard deviation. Statistical significance was indicated when P values were less than 0.05.

Results

Clinical features at presentation

Table 1 summarizes the main clinical and pathologic characteristics of patients with OB-FSG. All patients were Caucasians. Most of them (nine cases, 60%) had class I obesity (BMI 30–34.9 kg/m²), three (20%) had class II obesity (BMI 35–39.9 kg/m²) and the remaining three patients (20%) had class III or ‘morbid’ obesity (BMI > 40 kg/m²). At presentation, five patients (33%) (patients 11–15, Table 1) showed renal insufficiency and eight (53%) had hypertension.

Mean 24-h proteinuria was 3.1 ± 2 g (0.9–8.7 g/24 h). Although six patients (40%) showed nephrotic-range proteinuria (≥3.5 g/24 h), serum albumin and serum total proteins were normal in every case, and there were no indications of nephrotic syndrome (hypoproteinemia, hypoalbuminaemia, severe hyperlipidaemia). In addition, none of the patients, even those with nephrotic-range proteinuria, showed oedema on physical examination nor noticed oedema prior to the onset of follow-up.

Table 2 shows the clinical characteristics of I-FSG patients at presentation. All were Caucasians. The main differences between OB-FSG and I-FSG are shown in Table 3. I-FSG patients were younger and most had oedema as their initial symptom. Proteinuria values were significantly higher in I-FSG patients. In sharp contrast with OB-FSG patients, all I-FSG patients with nephrotic-range proteinuria showed oedema, hypoalbuminaemia, and hyperlipidaemia (Table 3).

In six patients with OB-FSG (40%), sleep-apnea syndrome was diagnosed before the performance of renal biopsy. In the remaining patients, there had been no analysis of the possible existence of sleep-apnea disorders. By definition, no patient had a history of diabetes, liver diseases, or systemic disorders. Renal echography at presentation revealed in 11 cases that both kidneys showed complete morphologic normality. In two patients, unilateral small kidneys compatible with the diagnosis of unilateral renal hypoplasia were detected. In another two patients, unilateral renal agenesis was detected by echography. Therefore, four patients with OB-FSG (26%) (patients 4, 10, 13 and 15,
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)/ Gender</th>
<th>BMI (kg/m²)</th>
<th>Weight (kg)</th>
<th>Height (m)</th>
<th>BP (mmHg)</th>
<th>Serum creatinine (mg/dl)</th>
<th>Proteinuria (g/24 h)</th>
<th>Per cent glomeruli with FSGS/GGS</th>
<th>ACEI treatment</th>
<th>Follow-up (months)</th>
<th>Outcome</th>
<th>Other clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53/M</td>
<td>35</td>
<td>100/1.69</td>
<td>140/90</td>
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<td>8.7</td>
<td>100/0</td>
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<td>60</td>
<td></td>
<td>Death (carcinoma) with stable renal function (SCr 1 mg/dl)</td>
<td>Sleep-apnea. Diabetes from 50th month of follow-up</td>
</tr>
<tr>
<td>2</td>
<td>46/M</td>
<td>31.6</td>
<td>97/1.75</td>
<td>140/80</td>
<td>0.8</td>
<td>2</td>
<td>10/25</td>
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</tr>
<tr>
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<td>46/M</td>
<td>30.5</td>
<td>81/1.63</td>
<td>170/110</td>
<td>1.1</td>
<td>3.9</td>
<td>18/18</td>
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</tr>
<tr>
<td>4</td>
<td>41/F</td>
<td>40.5</td>
<td>90/1.49</td>
<td>130/90</td>
<td>1.1</td>
<td>3</td>
<td>21/10</td>
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<tr>
<td>5</td>
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<td>70/1.50</td>
<td>120/80</td>
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<td>1.4</td>
<td>16/0</td>
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<td>Diabetes from 120th month of follow-up</td>
</tr>
<tr>
<td>6</td>
<td>56/M</td>
<td>32.5</td>
<td>94/1.70</td>
<td>105/60</td>
<td>1.1</td>
<td>3.5</td>
<td>30/0</td>
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</tr>
<tr>
<td>7</td>
<td>51/F</td>
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<td>91/1.65</td>
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<td>0.9</td>
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<td>Diabetes from 24th month of follow-up</td>
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<tr>
<td>8</td>
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<td>86/1.59</td>
<td>150/90</td>
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<td>1.4</td>
<td>10/20</td>
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<td>Stable renal function (SCr 1 mg/dl)</td>
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<td>3.2</td>
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<td>42.8</td>
<td>103/1.55</td>
<td>140/70</td>
<td>2</td>
<td>1.4</td>
<td>18/26</td>
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<td>36.2</td>
<td>111/1.75</td>
<td>180/100</td>
<td>2.5</td>
<td>5.4</td>
<td>16/60</td>
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<td>Unilateral renal hypoplasia</td>
</tr>
<tr>
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<td>49/F</td>
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<td>130/90</td>
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<td>4.6</td>
<td>10/50</td>
<td>Yes (2)</td>
<td>36</td>
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<td>Chronic dialysis</td>
<td>Sleep-apnea</td>
</tr>
<tr>
<td>14</td>
<td>66/M</td>
<td>31.6</td>
<td>86/1.65</td>
<td>150/100</td>
<td>3</td>
<td>3.9</td>
<td>29/50</td>
<td>No</td>
<td>36</td>
<td></td>
<td>Chronic dialysis</td>
<td>Unilateral renal hypoplasia</td>
</tr>
<tr>
<td>15</td>
<td>43/M</td>
<td>30.8</td>
<td>86/1.67</td>
<td>170/100</td>
<td>2.5</td>
<td>2.5</td>
<td>25/45</td>
<td>Yes (2)</td>
<td>60</td>
<td></td>
<td>Chronic renal insufficiency (SCr 5.8 mg/dl)</td>
<td>Unilateral renal hypoplasia</td>
</tr>
</tbody>
</table>

ACEI treatment: (1) denotes ACEI treatment from the onset of follow-up. (2) ACEI treatment started when renal function had already deteriorated.
Table 1) had reduced functional renal mass of probable congenital origin.

**Renal biopsy findings and clinico-pathologic correlations**

By light microscopy, the total number of glomeruli sampled in OB-FSG patients ranged from 6 to 60 (mean 18 ± 19). As is shown in Table 1, 6–100% of the glomeruli (mean 19 ± 23%) showed FSG lesions. The percentage of globally sclerotic glomeruli (GGS) ranged from 0 to 60% (mean 18 ± 18%). There was significant correlation between the percentage of glomeruli with FSG and 24 h proteinuria (r = 0.69, P < 0.05). The percentage of glomeruli with GGS was significantly correlated with serum creatinine (r = 0.83, P < 0.05) and creatinine clearance (r = −0.83, P < 0.05). Mean glomerular diameter was 256 ± 24 mm (192–280 μm), which was significantly greater than in I-FSG specimens. There were no significant differences in the percentage of glomeruli with FSG or GGS lesions between OB-FSG and I-FSG (Table 4). In OB-FSG, the severity of interstitial fibrosis, tubular atrophy, and arteriolosclerosis, graded from 0 to +4, was 2.2 ± 0.8, 2.2 ± 0.8, and 2.4 ± 0.8, respectively, and there were no differences compared with I-FSG.

**Clinical outcome and therapy**

The mean follow-up of OB-FSG patients, estimated up to the last visit, to death or to onset of chronic dialysis, was 82 ± 57 months (range 36–204 months). The mean follow-up of I-FSG patients was 64 ± 38 months (30–190 months).

In spite of recommendations for strict hypocaloric diets in OB-FSG patients, none showed sustained body weight reduction. BMI at the end of follow-up was 34.6 ± 4.2 kg/m² (27.5–45.2) with no change compared with initial BMI (35 ± 5.2 kg/m²). A positive correlation was found between BMI throughout follow-up and proteinuria values (r = 0.45; P < 0.05). No correlations were found between BMI and the number of sclerosed glomeruli, severity of tubular atrophy, interstitial fibrosis, or arteriolosclerosis. Blood pressures were controlled throughout follow-up among OB-FSG patients, although the patients were treated with antihypertensive drugs (12 patients with hypertension were treated with ACEI in an attempt to decrease proteinuria).

Proteinuria did not vary in OB-FSG during the follow-up. At the end of follow-up, it was 4.1 ± 3.3 g/24 h, and did not change from initial values (3.1 ± 2 g/24 h) (Table 3). The introduction of ACEI in 12 patients (at the onset of follow-up in eight cases and later in another four patients, see Table 1) was associated with a decrease in proteinuria during the first 6 months of treatment (Figure 1); it decreased from 4.6 ± 3.3 g/24 h at baseline to 2.1 ± 1.8 g/24 h at the third month and to 2.4 ± 1.3 g/24 h at the sixth month. However, proteinuria progressively increased in most patients, reaching values not different from baseline after the first 12 months of ACEI treatment. In eight out of 12 patients, the loss of the ACEI anitproteinuric effect coincided with body weight increases. Urinary sodium excretion, measured in eight out of 12 patients treated with ACEI, did not change after the introduction of ACEI (140 ± 55 mEq/24 h before ACEI; 132 ± 51 mEq/24 h after 6 months of treatment and 151 ± 49 mEq/24 h 12 months after ACEI introduction).

Proteinuria reached the nephrotic range (≥3.5 g/24 h) at presentation or during the follow-up in 12 patients (80%). Six patients (40%) showed proteinuria > 7.5 g/24 h during evolution, and in three of them it reached values persistently higher than 10 g/24 h; the highest proteinuria (20–25 g/24 h during 18 months) was in a male patient with BMI of 46 kg/m². In spite of these massive proteinuria values, none of the patients developed oedema, hypoproteinaemia nor hypoalbuminaemia, throughout follow-up.

Serum creatinine increased in OB-FSG patients from 1.5 ± 0.7 mg/dl at presentation to 3.9 ± 3.6 mg/dl at the end of follow-up (P < 0.001), and creatinine clearance decreased from 91 ± 44 to 65 ± 55 ml/min.
(P < 0.01). Eight patients (cases 1–8, Table 1) maintained a normal renal function after 85 ± 64 months of follow-up, without any indication of renal function deterioration. In contrast, the other seven patients showed a progressive renal insufficiency. At the end of follow-up, five patients (33%) were on chronic dialysis, two (13%) showed advanced renal insufficiency, and eight (53%) maintained normal renal function. By Kaplan–Meier analysis, the estimated probability of renal survival, without chronic dialysis, was 77 and 51% after 5 and 10 years of follow-up, respectively (Figure 2). In I-FSG, these values were significantly lower (52 and 30%, respectively). Among I-FSG patients, nine (60%) received immunosuppressive treatments (steroids alone in five, steroids plus chlorambucil in eight, and steroids plus cyclosporin in one). No patient with OB-FSG received immunosuppressive drugs.

The characteristics of OB-FSG patients with stable renal function or with progressive renal failure are shown in Table 5. The only differences at presentation were found in serum creatinine and creatinine clearance. All patients with stable renal function had normal values of serum creatinine at presentation, whereas five out of the seven patients that progressed towards renal failure had already showed renal insufficiency at presentation. Patients with a progressive decline in renal function also showed a higher percentage of GGS and higher degrees of interstitial fibrosis and tubular atrophy in renal biopsies. On univariate analysis, the risk of progression of renal insufficiency was correlated with serum creatinine (P < 0.0001, odds ratio 1.34, 95% CI 0.91–2) and creatinine clearance (P < 0.0001, odds ratio 1.26, 95% CI 0.89–1.78) at the onset of follow-up, whereas other clinical and pathological variables did not show statistical significance.

Three out of the four patients with reduced renal mass (patients 10, 13 and 15, Table 1) showed a progressive derangement in renal function. Two of them (cases 13 and 15) already had advanced renal insufficiency at presentation. There were no differences in the rate of renal failure progression compared with patients with normal renal mass.

Treatment with ACEI was not renoprotective, however, it should be noted that 12 of 15 (80%) patients received these drugs at differing periods of their follow-up. All cases in whom renal function remained normal during follow-up were treated with ACEI from the onset of follow-up, when renal function was still normal. On the contrary, the seven patients with progressively worsening renal function began ACEI when renal function had already deteriorated (four patients, numbers 9, 12, 13 and 15, Table 1) or did not receive these drugs during follow-up (patients 10, 11 and 14, Table 1).

Six patients (numbers 1, 4, 5, 7, 8 and 9, Table 1) developed progressive hyperglycaemia at 24–120 months of follow-up (mean 53 ± 39 months), and later required oral antidiabetic agents. The revision of renal biopsies performed at the onset of follow-up showed no morphologic criteria (light microscopy as well as
Table 4. Renal biopsy findings in OB-FSG and I-FSG

<table>
<thead>
<tr>
<th></th>
<th>Per cent of normal glomeruli</th>
<th>Per cent of glomeruli with FSG lesions</th>
<th>Per cent of glomeruli with GGS</th>
<th>Glomerular diameter (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OB-FSG (n = 15)</td>
<td>61 ± 24</td>
<td>19 ± 23</td>
<td>18 ± 18</td>
<td>256 ± 24</td>
</tr>
<tr>
<td>I-FSG (n = 15)</td>
<td>57 ± 20</td>
<td>24 ± 12</td>
<td>18 ± 20</td>
<td>199 ± 26</td>
</tr>
</tbody>
</table>

Fig. 1. Evolution of proteinuria after ACEI treatment in obesity-associated FSG.

Fig. 2. Renal survival in patients with obesity-associated FSG (OB-FSG) and idiopathic FSG (I-FSG). Numbers in brackets represent the patients at risk at every period of follow-up.

Discussion

Proteinuria is a recognized complication of obesity, and FSG is the most common pathological lesion found in these patients [12]. Clinical and histopathologic information about obesity-related proteinuria and FSG have been derived from case reports and autopsy studies, but the number of published cases with accurate clinical descriptions and biopsy-proven diagnosis is rather low [1–11]. Particularly scanty is information about the long-term outcome of this clinical entity. As follow-up description in most patients is missing, the development of renal insufficiency appeared to be uncommon.

The present study provides the largest clinical series of biopsy-proven OB-FSG published thus far. Based on prolonged follow-up, we revealed that this clinicopathological entity has a far from benign prognosis. Thus, for instance, a considerable proportion of our patients (33%) already showed renal insufficiency at presentation. At the end of follow-up, five out of 15 patients (33%) were on chronic dialysis and another two (13%) showed advanced chronic renal insufficiency. By Kaplan–Meier analysis of our series, the estimated probability of renal survival was 77% after 5 years of follow-up and 51% after 10 years. Although renal survival was significantly worse among patients with I-FSG (Figure 2), our data show for the first time that OB-FSG is a serious disease with a relatively poor prognosis.

The progression of renal insufficiency was statistically correlated with renal function (serum creatinine and creatinine clearance) at presentation. However, other clinical and laboratory parameters failed to correlate. All patients [8] with stable renal function throughout follow-up showed normal renal function at presentation; in addition, ACEI treatment was initiated at follow-up onset in all of them. In contrast, patients with an unfavourable evolution had already showed renal insufficiency at presentation, or ACEI treatment was prescribed when renal function had already deteriorated (Table 1). These data suggest that ACEI may halt the progression of renal insufficiency in patients with OB-FSG, but only when renal function is still normal. In a previous study, we reported a dramatic short-term antiproteinuric effect of captopril in eight patients with obesity-related proteinuria (FSG demonstrated by renal biopsy in one of them) [10]. In the present study, we confirmed the short-term antiproteinuric response to ACEI, with a significant proteinuria decrease after 3 and 6 months of treatment. However, a late proteinuria rebound was observed, with values returning to baseline after 12 months of treatment (Figure 1). This escape from the antiproteinuric effect of ACEI coincided with weight increases in many patients. As most studies have related the renoprotective benefits of ACEI to their antiproteinuric action [13–16], prospective studies are needed to assess the long-term efficacy of renin–angiotensin system blockade in OB-FSG.
Although weight loss represents another logical therapeutic approach in this entity, clinical available information about this issue is scarce. There are no clinical studies that have addressed long-term consequences of weight loss in proteinuric obese patients. In the present study, none of the OB-FSG patients showed sustained weight loss following our dietetic recommendations. This fact illustrates the difficulty in obtaining significant and sustained weight loss in most obese patients.

Our study demonstrated that patients with OB-FSG exhibit a distinctive clinical profile that is very useful for performing a differential diagnosis between this entity and other glomerular diseases. First, the appearance and progression of markers of renal disease (proteinuria, increasing serum creatinine) were slow in all our patients. Second, nephrotic-range proteinuria (presented in 80% of the patients at some time of evolution) was never accompanied by the typical findings of nephrotic syndrome (oedema, hypoalbuminaemia, extreme hyperlipidaemia) in spite of impressive proteinuria values (higher than 20 g/24 h) in some cases. In contrast, most patients with I-FSG exhibited sudden onset of nephrotic-range proteinuria, with hypoalbuminaemia and oedema. The peculiar discrepancy between high proteinuria and absence of oedema in our patients with OB-FSG illustrates the fact that renal disease is frequently detected only when chronic renal insufficiency is already established. In fact, both proteinuria and renal insufficiency were detected by chance upon routine medical checkups in our patients.

The reasons why obese patients with nephrotic proteinuria do not develop oedema are unknown. In a previous study, we showed that this characteristic is shared by other renal diseases secondary to hyperfiltration, such as reflux nephropathy or FSGS secondary to renal mass reduction [17]. We have previously reported that patients with massive proteinuria but without hypoalbuminaemia, as observed in hyperfiltrating disorders, have significantly lower urinary excretions of N-acetyl-B-glucosaminidase and β2-microglobulin than patients with hypoalbuminaemia [18]. These differences may suggest an altered tubular handling of filtered proteins in hyperfiltering disorders. In addition, the slow increase in proteinuria, characteristic of OB-FSG, may play an important role in the absence of hypoalbuminaemia and oedema, allowing compensatory mechanisms to counterbalance proteinuria.

The pathogenic mechanisms through which obesity can induce proteinuria and glomerulosclerosis are incompletely understood. However, several studies have demonstrated that obese patients show characteristic haemodynamic changes of glomerular hyperfiltration, including vasodilation of glomerular afferent arterioles with increased glomerular filtration rates and increased filtration fraction [19–21]. The characteristic insulin resistance and hyperinsulinaemia of obese patients could play a fundamental role in the pathogenesis of these haemodynamic changes [19–22]. In addition, insulin can increase the synthesis of several growth factors that induce glomerular sclerosis and hypertrophy [23]. Although we observed no clinical or pathological data indicating diabetes in our patients at presentation, six (40%) of them developed type II diabetes upon follow-up, emphasizing the relationship between obesity, insulin resistance and type II diabetes. The clinical similarities between our patients with OB-FSG and those with renal diseases mediated by hyperfiltration, such as reflux nephropathy or FSG associated with renal mass reduction (slowly progressive proteinuria and renal insufficiency, absence of hypoalbuminaemia despite massive proteinuria values) [12,17,24,25], support the role of glomerular hyperfiltration in the pathogenesis of OB-FSG. Furthermore, the pathological findings in our patients were similar to those found in hyperfiltrating diseases; for instance, the mean glomerular diameters (256 ± 24 mm, ranging from 192 to 280 mm) in our OB-FSG patients were significantly greater than in I-FSG. Glomerular hypertrophy is a common finding in renal diseases mediated by hyperfiltration [17].
Four (26%) of our OB-FSG patients had a reduced renal mass, which was due to unilateral renal agenesis in two cases and unilateral hypoplasia in the other two. Although FSG is a recognized complication of these congenital renal abnormalities [24] we speculate that obesity has a detrimental influence in patients with a reduced number of functioning nephrons. In this sense, we recently reported that obesity is a significant risk factor for the appearance of proteinuria and renal insufficiency after unilateral nephrectomy [26]. Three out of four patients in the current study with OB-FSG and a reduced renal mass showed a progressive renal insufficiency, although two (patients 13 and 15, Table 1) had already presented advanced renal impairment at diagnosis. The rate of renal failure progression in patients with reduced renal mass was similar to that of patients with normal renal mass.

Hyperlipidaemia is frequently observed in obese patients and a variety of experimental studies have shown that dyslipidaemia can contribute to renal injury. The importance of hyperlipidaemia in the pathogenesis of glomerulosclerosis has been demonstrated in the obese Zucker rat, a model of obesity, hyperinsulinaemia, and hyperlipidaemia, that develops glomerulosclerosis and progressive renal failure [27]. Treatment of hyperlipidaemia reduces glomerular injury in obese Zucker rats and in other experimental models of chronic renal failure [28,29]. We found no correlation between serum lipid levels and evolution of renal function; however, it is likely that a larger number of cases is necessary to accurately assess the role of lipids in OB-FSG.

We found a high prevalence of sleep-apnea syndrome among our OB-FSG patients. This diagnosis had been established before renal biopsy in six (40%) of our cases and it is possible that the prevalence may have been higher because sleep breathing studies were not performed in the remaining patients. Sleep apnea can induce sympathetic activation of the renin–angiotensin system and glomerular hypertension and FSG lesions with glomerulomegaly that are associated with this syndrome have been reported [6,7]. Interestingly, oxygen treatment decreased proteinuria in patients with sleep apnea syndrome [30].

In conclusion, we demonstrated that patients with OB-FSG have several distinctive clinical and pathologic features that distinguish this entity from other causes of FSG. The long-term outcome of our patients, which includes a frequent progression towards advanced renal failure, emphasizes the importance of an accurate early diagnosis of this entity. Prospective studies to assess the influence of therapeutic interventions (weight loss, blockade of renin–angiotensin system) are warranted.

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