

## Minimal change disease and focal segmental glomerulosclerosis in adults: response to steroids and risk of renal failure

### Authors

Lúcio R. R. Moura <sup>1</sup>  
 Marcello F. Franco <sup>2</sup>  
 Gianna Mastroianni  
 Kirsztajn <sup>2</sup>

<sup>1</sup> Hospital Israelita Albert Einstein.

<sup>2</sup> Universidade Federal de São Paulo.

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### Correspondence to:

Gianna Mastroianni Kirsztajn.  
 Disciplina de Nefrologia  
 (Departamento de Medicina) -  
 UNIFESP.  
 Rua Botucatu, nº 740, São Paulo,  
 SP, Brasil.  
 CEP: 04023-900.  
 E-mail: gm.kirsztajn@unifesp.br

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### ABSTRACT

**Introduction:** There is scarce data on the clinical profile of adult Brazilian patients with nephrotic syndrome caused by minimal change disease (MCD) and focal segmental glomerulosclerosis. **Objective:** We evaluated the clinical characteristics and response to treatment in adult patients with nephrotic syndrome having a histological diagnosis of MCD or FSGS. **Methods:** This is a retrospective analysis of 50 patients with MCD and 120 with FSGS. All patients were initially treated with steroids. The study outcomes were: steroid responsiveness, prevalence of total remission, progression to chronic renal failure and need of renal replacement therapy due to end-stage renal disease (ESRD). **Results:** Initial serum creatinine level was 24% higher among patients with FSGS ( $p = 0.02$ ), and proteinuria levels were 36% higher in MCD ( $p < 0.001$ ). Patients with MCD were sensitive to steroid therapy in 80% of the cases, with total remission in 74%, while patients with FSGS were sensitive in 58% ( $p = 0.01$ ), with total remission in 30% ( $p = 0.002$ ). Patients with FSGS had an acute renal failure prevalence of 39% (*vs.* 12%,  $p = 0.013$ ) and ESRD of 10% (*vs.* 0%,  $p < 0.001$ ). Steroid responsiveness reduced in 83% the risk of ESRD ( $p < 0.001$ ), while total remission was associated to a reduction in risk of 89% ( $p < 0.001$ ). **Conclusion:** A positive response to steroid therapy was the most important factor related with preservation of renal function and FSGS was related with less steroid responsiveness.

**Keywords:** glomerulosclerosis, focal segmental; glucocorticoids; nephrotic syndrome; renal insufficiency; steroids; therapeutics.

### INTRODUCTION

Nephrotic syndrome is one of the main presentations of glomerular diseases and such manifestation, when persistent, is associated with progression to stage 5 chronic kidney disease (5-CKD).<sup>1</sup> Several histological abnormalities may lead to the development of nephrotic syndrome,<sup>2,3</sup> and what stands out as a cause of idiopathic nephrotic syndrome is minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). In children, MCD is the cause of nephrotic syndrome in 90% of patients,<sup>4,11</sup> while adults have about 30% of associated systemic diseases (e.g. diabetes, amyloidosis and lupus erythematosus)<sup>4</sup>, and the other 70% are represented by primary glomerular diseases such as FSGS, membranous glomerulonephritis or even MCD.<sup>4,5,12</sup>

When considering only the adult population, FSGS is the main cause of the syndrome in several countries, including Brazil.<sup>4,5,13,14</sup> We must remember that FSGS may be the morphological expression of a number of disorders characterized mainly by podocyte injury,<sup>15</sup> which may be due to the presence of a circulating permeability factor, genetic mutations that affect proteins in the podocyte slit diaphragm, viral infections, toxic agents, hyperfiltration, among other possible causes.<sup>16-18</sup> FSGS has been recognized as a primary disease in the

late 1950<sup>19</sup> and has been considered by some researchers as part of a spectrum of podocyte diseases, whose extremes are the MCD and the very FSGS.<sup>20-22</sup> If there indeed is a progression of MCD to FSGS, it is still a matter of controversy, but certainly these ailments share many features as some etiologic factors, justifying them to be seen as a complex of glomerular diseases. Yet, from the therapeutic point of view, there are differences in drug regimens upon diagnosis, at least in regards to the duration of the attack phase in the case of corticotherapy, as well as the response rate to treatment and prognosis.

In the present study, we evaluated the clinical characteristics and response to treatment with corticosteroids in adult patients with proteinuria and histological diagnosis of MCD or FSGS. We consider these entities as independent diseases in order to evaluate the main clinical and prognostic differences between them in an adult population.

## SAMPLE AND METHODS

This is a longitudinal retrospective study of a cohort of patients with MCD or FSGS diagnosis followed up in the Glomerulopathies Department of UNIFESP (Brazil) for six consecutive years. During this period, 192 patients were included in the study. It should be clarified that small children are not usually treated by our team, but patients with 12 years or more are followed up in our clinic.

Regarding histopathological evaluation, at least the analysis by light microscopy and immunofluorescence were performed in all renal biopsies. In addition, the following clinical and laboratory parameters were evaluated: age, gender, ethnicity, hypertension at diagnosis, initial levels of proteinuria and serum creatinine; the last two tests were also analyzed at the end of follow-up. It was considered as “progression to renal failure”, “double the initial serum creatinine or detection of levels above 2.0 mg/dL.”

All patients were initially treated with corticosteroids following the clinic’s protocol.

Partial remission was defined as 50% reduction in the initial proteinuria level, or levels below 2.0 g/24 hours. It was considered complete remission when proteinuria turned negative. In the absence of corticosteroid response after approximately four to six months of treatment with 1 mg/kg/day of prednisone orally, patients who were resistant to treatment with corticosteroids started being treated with cyclophosphamide or cyclosporine, according to the histological type and kidney function at the time, but the responses to these treatment modalities have not been evaluated in this study.

## OUTCOMES

We analyzed the following outcomes: response to corticosteroids (partial or complete remission), prevalence of complete remission, progression to renal failure and need for renal replacement therapy due to 5-CKD.

## STATISTICAL ANALYSIS

Categorical variables were presented as percentages and numerical variables as mean and standard deviation when the distribution was normal; or median and interquartile interval [Q1; Q3], when it was not normal. Normality was assessed by the Shapiro-Wilk test. Categorical variables were compared using the Fisher exact test or the chi square test. Numerical variables were compared using the Student *t*-test when the distribution of data was normal, or the Mann-Whitney test, in other cases. Multivariate analysis regarding the risk of developing renal failure was carried out by the Cox logistic regression. Statistical significance was defined as  $p < 0.05$ . For statistical analysis, we used the SPSS 17 for Windows.

## RESULTS

### DEMOGRAPHICS

Considering the 192 patients initially included in the present analysis, 50 had a diagnosis of MCD and 142 of FSGS. Subsequently, 22 cases of FSGS were excluded for being classified as

secondary FSGS. The demographic data is shown on Table 1, distributed according to histologic types of glomerulopathies.

In the primary FSGS group, the median age was 32 [22;44] years, 45% of patients were males, 40% were whites and 15.7% were blacks. The MCD patients were younger; however, this difference was not statistically significant; the median age was 27 [21;37] years ( $p = 0.07$ ). Among patients with MCD, 56% were males, 68% were whites and 6.1% blacks. Thus, there were no differences in the prevalence of gender and ethnicity in relation to the histological types of glomerulopathies. The prevalence of hypertension upon diagnosis was two times higher in patients with FSGS: 28% *vs.* 14% ( $p = 0.16$ ), yet this difference did not reach statistical significance.

#### CREATININE SERUM AND PROTEINURIA

Serum creatinine, during the initial stages of the disease, was 24% higher in patients with FSGS (Figure 1). The initial serum creatinine of the MCD group was  $1.17 \pm 0.53$  mg/dL, while the group with FSGS had  $1.53 \pm 0.96$  mg/dL ( $p = 0.02$ ). All patients had nephrotic syndrome at some point in the course of follow-up and initial levels of 24-hour proteinuria were 36% higher among patients with MCD: 7.01 [4.19, 10.37] *vs.* 4.19 [2.18; 6.56] g ( $p < 0.001$ ).

#### RESPONSE TO CORTICOSTEROIDS

Eighty percent of patients with MCD were considered sensitive to the instituted steroid therapy: 74% had complete remission and 6% partial. On the other hand, only 58.4% of those with FSGS were responsive to such treatment ( $p = 0.01$ ): complete remission was observed in 30.0% ( $p = 0.002$ ) and partial remission in 28.4%. There were 13 relapses after corticosteroid therapy in the MCD group and 14 in the FSGS group. Six patients with MCD (12%) had renal failure at diagnosis or upon follow up, with all these cases associated to hypovolemia, leading to pre-renal acute renal failure and possibly acute tubular necrosis (a condition clinically suspected,

but not usually confirmed by renal biopsy, since this procedure was not indicated for this specific purpose); dialysis was not needed in any case of MCD. It should be noted that in FSGS patients, the prevalence of renal failure was 39% (0.013), and 10% required dialysis ( $p < 0.001$ ), as shown in Figure 2. There were no deaths in the MCD group; but two (1.6%) occurred in the group with FSGS, although in any case the cause of death was associated with the kidney disease or the immunosuppressive therapy.

We evaluated the variables related to the risk of developing chronic renal failure in patients with FSGS (Table 2). In a multivariate analysis, a response to corticosteroids reduced by 83% the risk of chronic renal failure ( $p < 0.001$ ), and total remission, in turn, was associated with a reduced risk of about 89% ( $p < 0.001$ ).

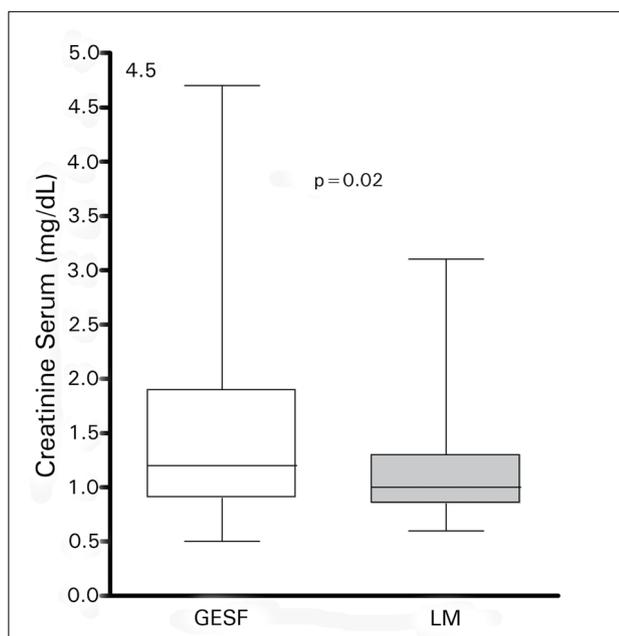
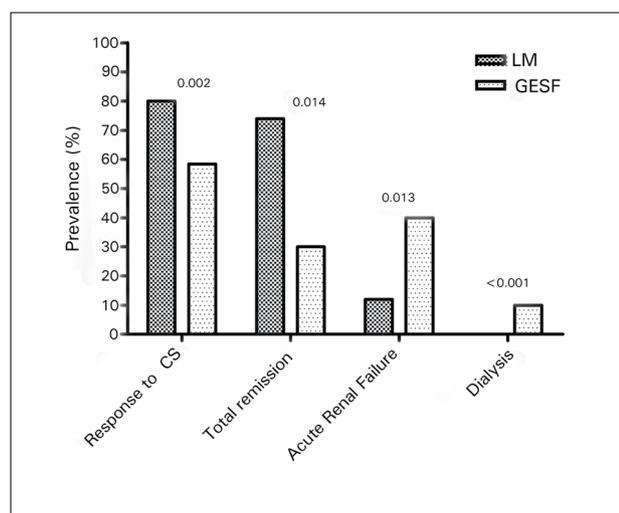
#### DISCUSSION

In many countries, including Brazil, FSGS is the leading cause of nephrotic syndrome in adults when considering only histologic diagnosis.<sup>14</sup> Some authors have reported that FSGS and MCD together are the most frequent causes of nephrotic syndrome in adults and children.<sup>4-8</sup> In a study carried out in our clinic, which involved the analysis of 9,617 biopsies of native kidneys, Polito *et al.*<sup>14</sup> found that FSGS accounted for 24.6% of primary glomerular diseases, ranking the first place in this group, as well as among the glomerular diseases presenting as nephrotic syndrome. The prevalence of FSGS as a cause of nephrotic syndrome was also demonstrated by us on the histological evaluation of adolescents with glomerular diseases.<sup>11</sup> Indeed, the increasing frequency of FSGS has been documented recently in several renal biopsy records.<sup>5-8,14</sup> It is important to remember that previously, membranous glomerulonephritis was the main cause of nephrotic syndrome in adults,<sup>23</sup> but now, although it predominates in some registers, it is recognized worldwide as the leading cause of nephrotic syndrome only in the elderly population.<sup>24,25</sup>

**TABLE 1** DEMOGRAPHICS OF PATIENTS WITH MCD AND FSGS

Variables	MCD	FSGS	p-value
Age (years)	27 [21;37]	32 [22;44]	0.07*
Ethnicity - Caucasian (%)	68%	40%	0.32
Gender - Male (%)	56%	45%	0.57
Arterial hypertension (%)	14%	28%	0.16
Serum creatinine (mg/dL)	1.17 ± 0,53	1.53 ± 0,96	0.016#
Proteinuria (g/24 hours)	7.01 [4.19;10.37]	4.19 [2.18;6.56]	< 0.001*

# Student t-test; \* Mann-Whitney

**Figure 1.** Creatinine serum levels upon disease onset in patients with MCD and FSGS.**Figure 2.** Main outcomes in the groups of patients with MCD and FSGS.

In the present study, we retrospectively evaluated the clinical characteristics and response to steroid therapy of patients with histological

**TABLE 2** RELATIVE RISKS OF PATIENTS WITH MCD AND FSGS DEVELOPING RENAL FAILURE

Variables	Relative risk	95% Confidence interval	p-value
Total remission	0.21	0.08-0.56	< 0.001
Response to corticosteroid	0.27	0.11-0.65	< 0.001

diagnosis of FSGS (N = 120) and primary MCD (N = 50) followed for over a decade. Since our clinic mainly sees adult patients, children have not been included in this analysis.

We noticed that FSGS patients were older than those with MCD. We did not find any difference as far as gender or ethnicity is concerned in both glomerulopathies. In fact, there are reports that MCD in childhood is more common in males, but there is apparently no gender difference in adults.<sup>12</sup> It is clear that in the United States there is a higher prevalence of African-Americans among patients with FSGS.<sup>26-28</sup> But this ethnic profile was not found in the group evaluated here nor in other Brazilian studies.<sup>8,14</sup> However, it must be clear that it is difficult to separate racial groups in our country, since most of the population is mixed.<sup>29</sup>

It is noteworthy that, during follow-up, all patients included in the study had nephrotic syndrome, and less than 10% in each group were submitted to renal biopsy when the proteinuria level was still less than 3.5 g/24h. It is known that less than 10% of MCD patients did not have nephrotic proteinuria when the disease manifested, while such percentage can reach 30% in FSGS patients.<sup>30,31</sup>

In our study, initial levels of proteinuria in patients with MCD (average 8.2 g/24h) were

higher than those with FSGS (average 5.3 g/24h). Waldman *et al.*<sup>32</sup>, analyzed 95 patients with MCD, and reported mean levels of proteinuria at 10 g/24h and serum creatinine of 1.4 mg/dL, similar to the levels detected by us (8.2 g/24h and 1,2 mg/dL, respectively). It describes an incidence of hypertension in adults with MCD that reaches 45% (32). In this study, 14% of patients had hypertension upon the diagnosis of MCD. This percentage is higher in cases of FSGS<sup>33,34</sup>, corresponding to 28% in our population.

Currently, it is clear that all patients with nephrotic syndrome by MCD or primary FSGS should be treated with corticosteroids or other immunosuppressants, as appropriate, since spontaneous remission is uncommon in both glomerular diseases<sup>21,35,36</sup> and there is, in the worst case scenario, a reasonable chance of remission with treatment. Without specific treatment, MCD is associated with increased risk of mortality from infectious diseases, thrombotic events and FSGS, with progression to 5-CKD.<sup>35,36</sup> Such progression is rare in patients with MCD and, when reported, most were cases that did not respond to corticosteroids or that were related to the diagnosis of FSGS in biopsies performed at a later stage in the evolution of the disease.<sup>37,38</sup> As to be expected, in none of our patients with MCD, there was progression to 5-CKD, although 10% of them developed acute renal failure at presentation or during follow up. Acute renal failure in MCD is related to the reduction in effective blood volume or acute tubular necrosis, and an incidence of up to 18% has been described.<sup>32</sup>

Today, it is a consensus that corticosteroids are the drugs of first choice to start treatment of both MCD and FSGS, and a more prolonged course of corticosteroid therapy in the case of FSGS is indicated.<sup>35,36</sup> Patients included in this analysis were initially treated with prednisone 1 mg/kg/day orally. Eighty percent of the MCD cases achieved remission (74% complete remission), as well as 58% of those with FSGS. Response rates to corticosteroids were similar to other studies, i.e. 80 to 95% in MCD and 15 to 60% in FSGS.<sup>21,32,37-44</sup>

As per demonstrated here, the response to corticosteroids in the course of MCD and FSGS is very significant. A response to corticosteroids represented an 83% risk reduction when assessing the tendency to progression to 5-CKD, and this reduction reached 89% when there was total nephrotic syndrome remission, confirming the importance of this type of treatment in this group of patients to avoid loss of renal function. Several studies in other population groups have confirmed that the response to corticosteroids is the main factor affecting the course of FSGS,<sup>37-44</sup> as corroborated by us now.

Finally, in the present study, we describe the clinical profile of Brazilian patients with MCD and FSGS, whose disease is presented as nephrotic syndrome in adults and underwent treatment with corticosteroids, demonstrating the sharp protective role of this therapy during follow-up, which lasted for more than a decade, with a success rate similar to that observed worldwide.

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