Differences between Primary and Secondary FSGS: Clinical and therapeutic implications

Manuel Praga
Head of Nephrology Department, Hospital 12 de Octubre, Madrid
Professor of Medicine, Complutense University of Madrid

Summary. The different causes of FSGS can be separated into (1) primary or idiopathic cases (2) genetic diseases affecting the expression and function of essential podocyte proteins (podocin, nephrin, alpha-actinin-4, the TRPC6 ion channel, CD2AP, synaptopodin) and (3) secondary FSGS (1,2) (Slight 2). Viral infections (e.g HIV nephropathy), drug toxicity (pamidronate, interferon, adriamycin), malignancies and heroin nephrotoxicity are examples of secondary FSGS. However the commonest type of secondary FSGS is included under the name of adaptive or hyperfiltering FSGS (3). A characteristic profile of glomerular hemodynamics, resulting in preglomerular vasodilation and increased intracapillary hydrostatic pressure is thought to be the main responsible of these types of FSGS (4). Conditions associated with a very low number of nephrons (extreme surgical resections, renal agenesis, vesicoureteral reflux with extensive parenchymal scars) represent classic examples of hyperfiltering FSGS. However, obesity-related FSGS is currently the most frequent type of secondary FSGS, reflecting the current worldwide epidemic of obesity (5). Both clinical and experimental studies have demonstrated that obesity induces glomerular hyperfiltration through a number of pathophysiological mechanisms, although many of them remain only partially known (6) (Slights 3-5).

The distinction between the different types of FSGS is crucial, since their treatment is radically different (Slight 6). Immunosuppressive agents (steroids, anticalcineurinics, cytostatics) are the mainstay of treatment in primary forms, whereas a conservative approach is currently recommended in genetically-determined FSGS, given the lack of efficacy of immunosuppressants. Treatment of secondary FSG is based (in addition to the elimination of the main cause, if possible) on drugs that block the renin-angiotensin system (ACE inhibitors, angiotensin receptor antagonists, antialdosteronic agents). Other measures such as control of blood pressure, statins for the treatment of
hyperlipidemia, as well as the prevention of obesity, sedentarism and smoking are also very important.

The differential diagnosis should be established after a careful analysis of clinical and analytical data, including a detailed interrogation about family history, medications and possible toxic habits. A very early onset of disease and a family history of nephrotic syndrome should arise the suspicion of genetic FSGS. However, cases of adult-onset FSGS without clear antecedents have been reported in the last years. The presence of an obvious renal mass reduction or of obesity would orientate the diagnosis to hyperfiltering FSGS. However, given the current epidemic of obesity (Slight 7), the possibility of a primary or genetically determined FSGS in obese should be always kept in mind.

Some clinical y analytical data can be extremely helpful to differentiate primary or genetic forms of FSGS from hyperfiltering types (including obesity-related FSGS). An slow increase of proteinuria (in contrast with the rapid appearance of nephrotic syndrome in primary types) and the absence of hypoalbuminemia and edema even in the presence of massive proteinuria (opposed to the complete nephrotic syndrome that most of primary and genetic types develop) are very characteristic of hyperfiltering FSGS (7-8) (Slight 8-9). Histological findings very suggestive of hyperfiltering types are the presence of enlarged glomeruli and the irregular effacement of podocytes (9) (Slight 10).

Obesity-related FSGS can evolve towards ESRD and the response to RAS blockade is only partial in many patients (10) (Slight 11-12). On the other hand, weight loss (induced by hypocaloric diet or bariatric surgery) has shown an important antiproteinuric efficacy (11) (Slight 13). In addition to “pure” obesity-related FSGS, the presence of obesity might negatively influence the outcome of many other proteinuric kidney diseases. Recent studies have shown that the combination of obesity and reduced renal mass has a synergistic detrimental influence on long-term kidney function outcome (12,13) (Slight 14-15).

REFERENCES


Differences between Primary and Secondary FSGS
Clinical and therapeutic implications

Manuel Praga
Focal Segmental Glomerulosclerosis (FSGS)

- Genetic
- Primary (Idiopathic)
- Secondary
OBESITY-RELATED PROTEINURIA PATHOGENESIS

HYPERFILTRATION

Obese patients typically show the characteristic hemodynamic changes of hyperfiltration models:

- Preglomerular Vasodilation
- GFR Increase
- Filtration Fraction Increase
The effects of Weight Loss on renal function in patients with severe obesity
OBESITY-RELATED PROTEINURIA PATHOGENESIS

Increased Sodium tubular reabsorption

Increased sympathetic renal activity

Obesity-associated Hyperleptinemia

Activation of Renin-Angiotensin system

Obese Patients

↑ PRA
↑ Angiotensinógeno
↑ ECA
↑ Angiotensina II
↑ Aldosterone
TREATMENT OF FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS

**Idiopathic or Primary FSGS**
- ACEI or ARB
- Persistence of Nephrotic syndrome
  - Steroids for ± 6 months
    - No response
  - Cyclosporin or Tacrolimus
    - No response or intolerance to treatment
    - Mycophenolate

**Secondary FSGS**
- (Obesity, Reflux nephropathy, Reduced renal mass...)
- Therapy of the specific cause (if possible)
  - ACEI or ARB in increasing doses
  - Strict control of BP
  - Prevention and treatment of obesity
  - Treatment of hyperlipidemia
  - No smoking, physical exercise
  - Protein restriction (if CRF)

Aggressive course, no response to previous therapies
¿Plasmapheresis?


*Kidney International* 2001; 59:1498-1509
<table>
<thead>
<tr>
<th>Obesity-related FSGS</th>
<th>Primary FSGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Slowly increasing proteinuria</td>
<td>- Sudden onset of proteinuria</td>
</tr>
<tr>
<td>- Lower Proteinuria</td>
<td>- Higher Proteinuria</td>
</tr>
<tr>
<td>- Slow progression into ESRD</td>
<td>- Rapid progression of renal failure</td>
</tr>
<tr>
<td>- Glomerulomegaly</td>
<td>- Normal glomerular volume</td>
</tr>
<tr>
<td>- Irregular pedicelar fusion</td>
<td>- Diffuse pedicelar fusion</td>
</tr>
</tbody>
</table>
ABSENCE OF HYPOALBUMINEMIA DESPITE MASSIVE PROTEINURIA IN FOCAL SEGMENTAL GLOMERULOSCLEROSIS SECONDARY TO HYPERFILTRATION
Praga, E. Morales, JC Herrero, A Perez Campos, B. Domínguez-Gil, R. Alegre, J. Vara, MA Martínz
Am J Kidney Dis 33: 52-58, 1999

Table 1. Clinical Characteristics of Group I Hypoalbuminemic and Group II Normoalbuminemic Patients

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 19)</th>
<th></th>
<th>Group II (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>24 ± 16 (3-55)</td>
<td>41 ± 14* (18-67)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>12 M, 7 F</td>
<td>14 M, 4 F</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>19/19 (100%)</td>
<td>0/18† (0%)</td>
<td></td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>135 ± 26/85 ± 16</td>
<td>152 ± 30/90 ± 14</td>
<td></td>
</tr>
<tr>
<td>Proteinuria (g/24 h)</td>
<td>9.7 ± 3.6 (4.6-18)</td>
<td>6.7 ± 3† (3.7-16.9)</td>
<td></td>
</tr>
<tr>
<td>S Total Proteins (g/dL)</td>
<td>4.4 ± 0.5 (3.5-5.6)</td>
<td>6.7 ± 0.4† (6.1-7.6)</td>
<td></td>
</tr>
<tr>
<td>S Albumin (g/dL)</td>
<td>2 ± 0.3 (1.4-2.7)</td>
<td>4 ± 0.3† (3.6-4.6)</td>
<td></td>
</tr>
<tr>
<td>SCr (mg/dL)</td>
<td>1.1 ± 0.5 (0.5-2.6)</td>
<td>1.4 ± 0.8 (0.9-3.7)</td>
<td></td>
</tr>
<tr>
<td>CrCl (mL/min/1.73 m²)</td>
<td>86 ± 33 (33-140)</td>
<td>81 ± 42 (25-150)</td>
<td></td>
</tr>
<tr>
<td>S Cholest (mg/dL)</td>
<td>567 ± 199 (309-945)</td>
<td>250 ± 41† (181-330)</td>
<td></td>
</tr>
<tr>
<td>S Triglyc (mg/dL)</td>
<td>363 ± 185 (103-980)</td>
<td>193 ± 95* (66-450)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Values expressed as mean ± standard deviation (range).
Abbreviations: S, serum; SCr, serum creatinine; CrCl, creatinine clearance; S Cholest, serum cholesterol; S Triglyc, serum triglycerides.
* P < 0.01.
†P < 0.001.
Podocyte foot process effacement as a diagnostic tool in focal segmental glomerulosclerosis

Jeroen K.J. Deegens¹, Henry B.P.M. Dijkman², George F. Borm³, Eric J. Steenbergen², José G. van den Berg⁴, Jan J. Weening² and Jack F.M. Wetzels¹

Kidney International 2008; 74: 1568
CLINICAL FEATURES AND LONG-TERM OUTCOME OF OBESITY-ASSOCIATED FOCAL SEGMENTAL GLOMERULOSCLEROSIS
M. Praga, E. Hernández, E. Morales, A Pérez-Campos, MA Valero, MA Martínez, M. León
*Nephrol Dial Transplant 2001; 16: 1790-1798*

- Fifteen obese patients (BMI>30 Kg/m2) with FSG
- Follow-up 82±57 months (range 36-204)
- Seven (46%) patients showed progressive renal insufficiency, 5 of them starting chronic dialysis
- Serum creatinine at presentation associated with development of progressive renal failure
RENAL SURVIVAL (%)

YEARS

*Kidney Int 68:263-70, 2005*  

![Graph showing the probability of absence of proteinuria]  

Probability of absence of proteinuria in group 1 patients with BMI >25 Kg/m² (dashed line) and <25 Kg/m² (solid line) (p 0.0006).
Influence of Obesity on the appearance of Proteinuria and Renal Insufficiency after Unilateral Nephrectomy. 

**Body Mass Index of Patients with Uninephrectomy**

<table>
<thead>
<tr>
<th>Group I: Patients with hyperfiltration nephropathy</th>
<th>Group II: Patients with normal renal function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrectomy</td>
<td><strong>p&lt;0.001</strong></td>
</tr>
<tr>
<td>Follow-up</td>
<td><strong>p&lt;0.001</strong></td>
</tr>
<tr>
<td>Study</td>
<td><strong>p&lt;0.001</strong></td>
</tr>
</tbody>
</table>

**p<0.001**