

Differences between Primary and Secondary FSGS: Clinical and therapeutic implications

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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) (Sights 3-5).

The distinction between the different types of FSGS is crucial, since their treatment is radically different (Slight 6). Immunosuppressive agents (steroids, anticalcineurics, 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) (Slights 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) (Slights 14-15).

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La Coruña 2010**

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Secondary FSGS
Clinical and therapeutic
implications**

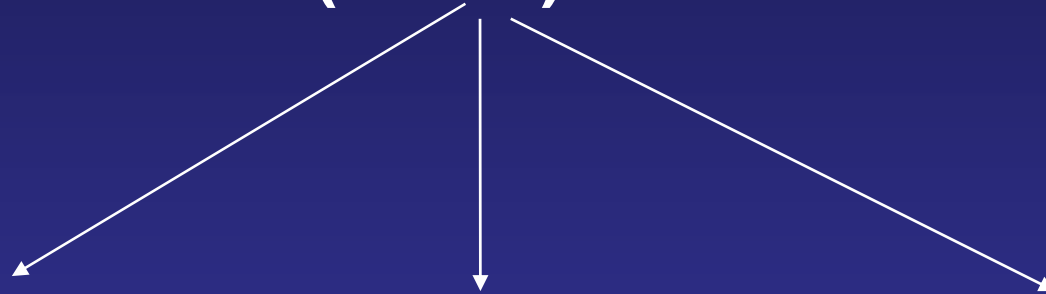
Manuel Praga

Focal Segmental Glomerulosclerosis (FSGS)

Genetic

Primary (Idiopathic)

Secondary



OBESITY-RELATED PROTEINURIA PATHOGENESIS

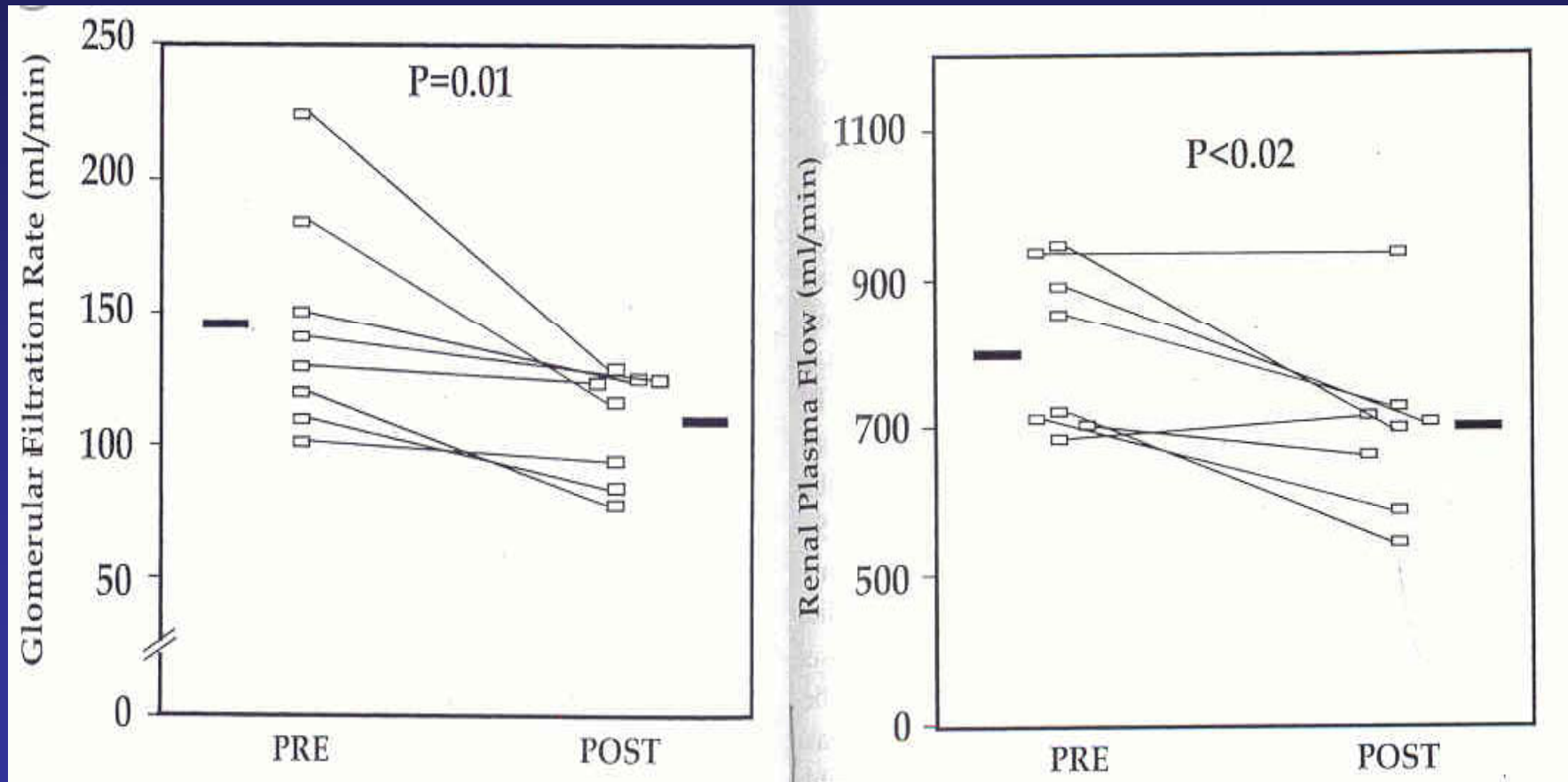
HYPERFILTRATION

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

Chagnac A et al. J Am Soc Nephrol 2003; 14:1480-86



OBESITY-RELATED PROTEINURIA PATHOGENESIS

Increased Sodium tubular reabsorption

Increased sympathetic
renal activity

Activation of
Renin-Angiotensin system

↑
Obesity-associated
Hyperleptinemia

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 I

Aggressive course, no response to previous therapies
¿Plasmapheresis?

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

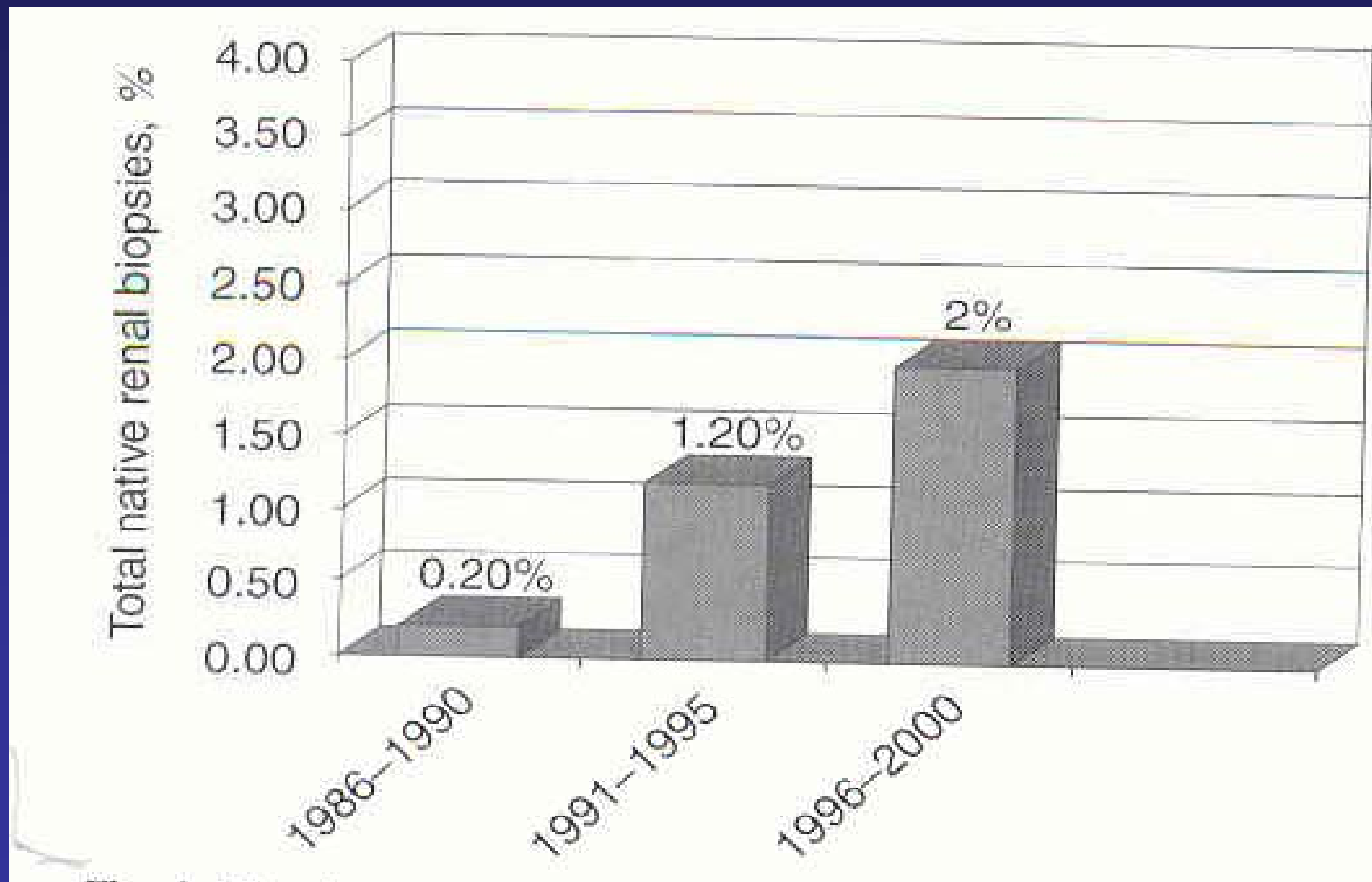
-No smoking, physical exercise

-Protein restriction (if CRF)

M. Praga. Treatment of focal segmental glomerulosclerosis.
Nefrología 25: 612-621, 2005.

Kambham N et al. Obesity-Related Glomerulopathy: An Emerging Epidemic.

Kidney International 2001; 59:1498-1509



Obesity-related FSGF vs primary FSGS

Obesity-related FSGS

- Slowly increasing proteinuria
- Lower Proteinuria
- Slow progression into ESRD
- Glomerulomegaly
- Irregular pedicelar fusion

Primary FSGS

- Sudden onset of proteinuria
- Higher Proteinuria
- Rapid progression of renal failure
- Normal glomerular volume
- Diffuse pedicelar fusion

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 Martínez
Am J Kidney Dis 33: 52-58, 1999

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

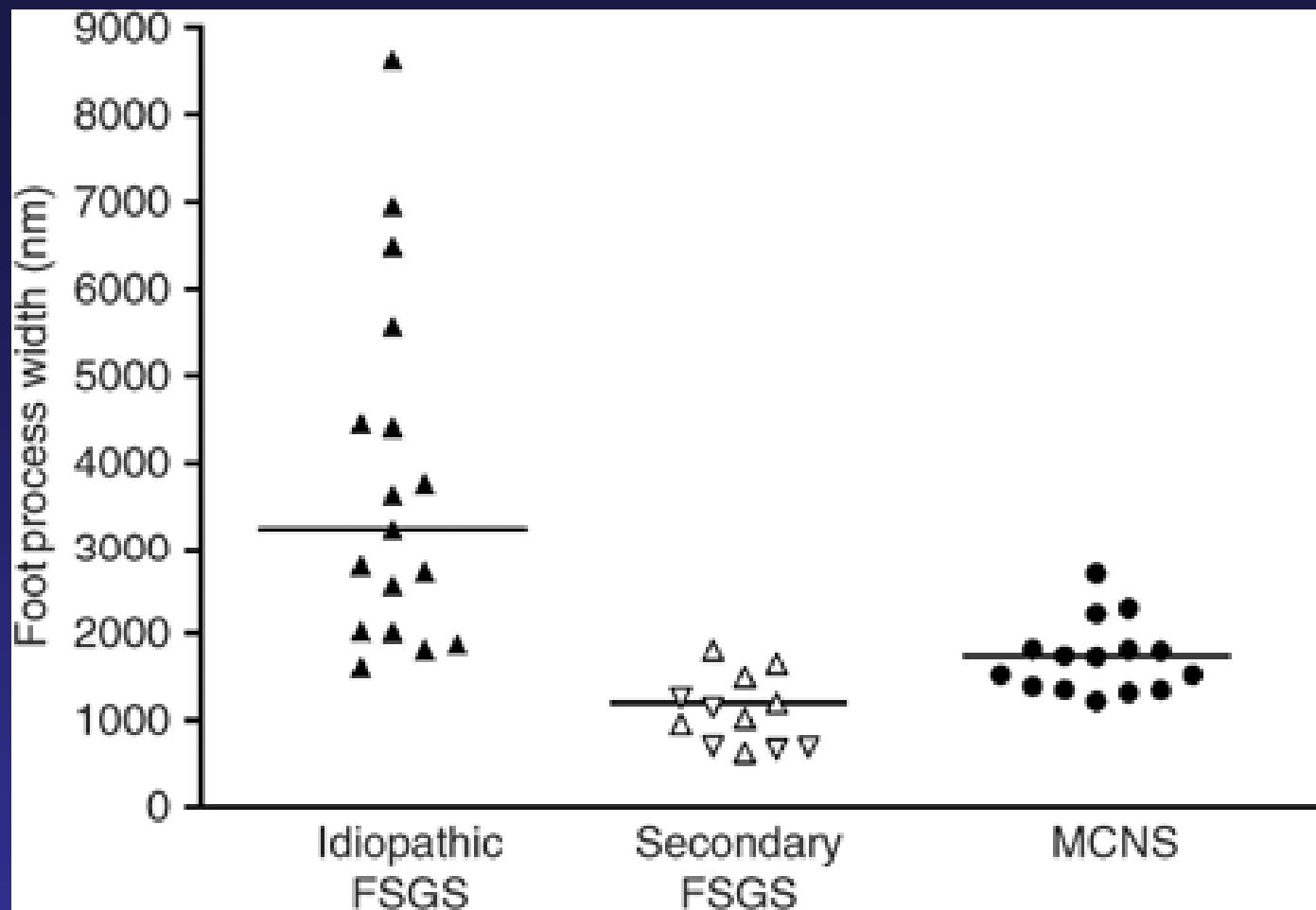
	Age (yr)	Sex	Edema	BP (mm Hg)	Proteinuria (g/24 h)	S Total Proteins (g/dL)	S Albumin (g/dL)	SCr (mg/dL)	CrCl (mL/min/1.73 m ²)	S Cholest (mg/dL)	S Triglyc (mg/dL)
Group I (n = 19)	24 ± 16 (3-55)	12 M, 7 F	19/19 (100%)	135 ± 26/85 ± 16	9.7 ± 3.6 (4.6-18)	4.4 ± 0.5 (3.5-5.6)	2 ± 0.3 (1.4-2.7)	1.1 ± 0.5 (0.5-2.6)	86 ± 33 (33-140)	567 ± 199 (309-945)	363 ± 185 (103-980)
Group II (n = 18)	41 ± 14* (18-67)	14 M, 4 F	0/18† (0%)	152 ± 30/89 ± 14	6.7 ± 3† (3.7-16.9)	6.7 ± 0.4† (6.1-7.6)	4 ± 0.3† (3.6-4.6)	1.4 ± 0.8 (0.9-3.7)	81 ± 42 (25-150)	250 ± 41† (181-330)	193 ± 95* (66-450)

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

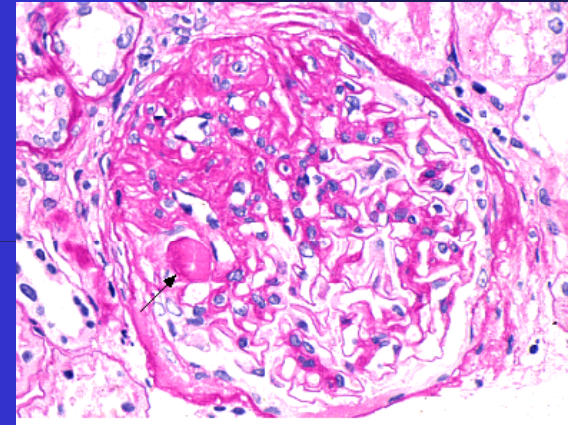
Jeroen K.J. Deegens¹, Henry B.P.M. Dijkman², George F. Borm³, Eric J. Steenbergen², José G. van den Berg⁴, Jan J. Weening² and Jack F.M. Wetzels¹

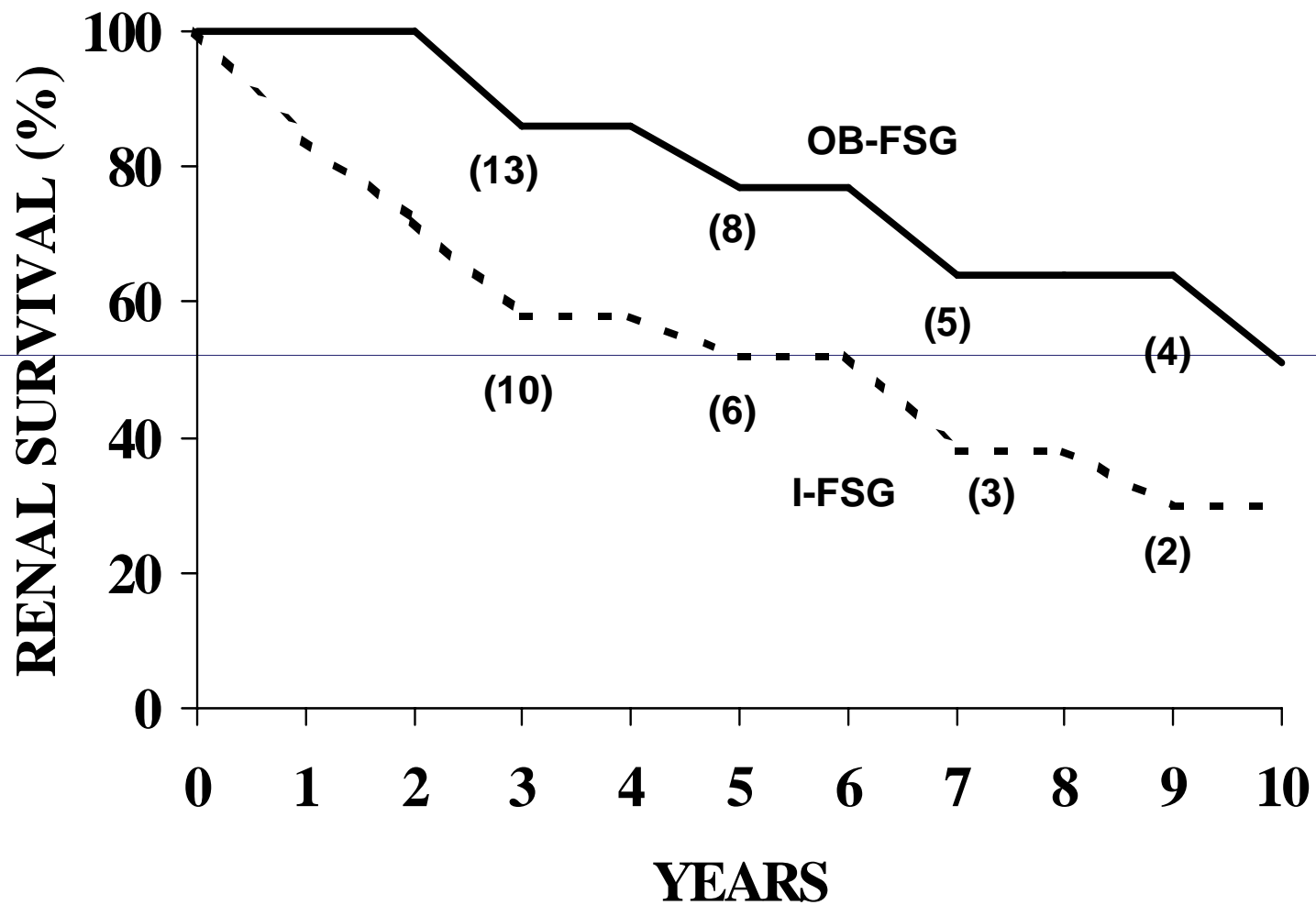
Kidney International 2008; 74: 1568

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

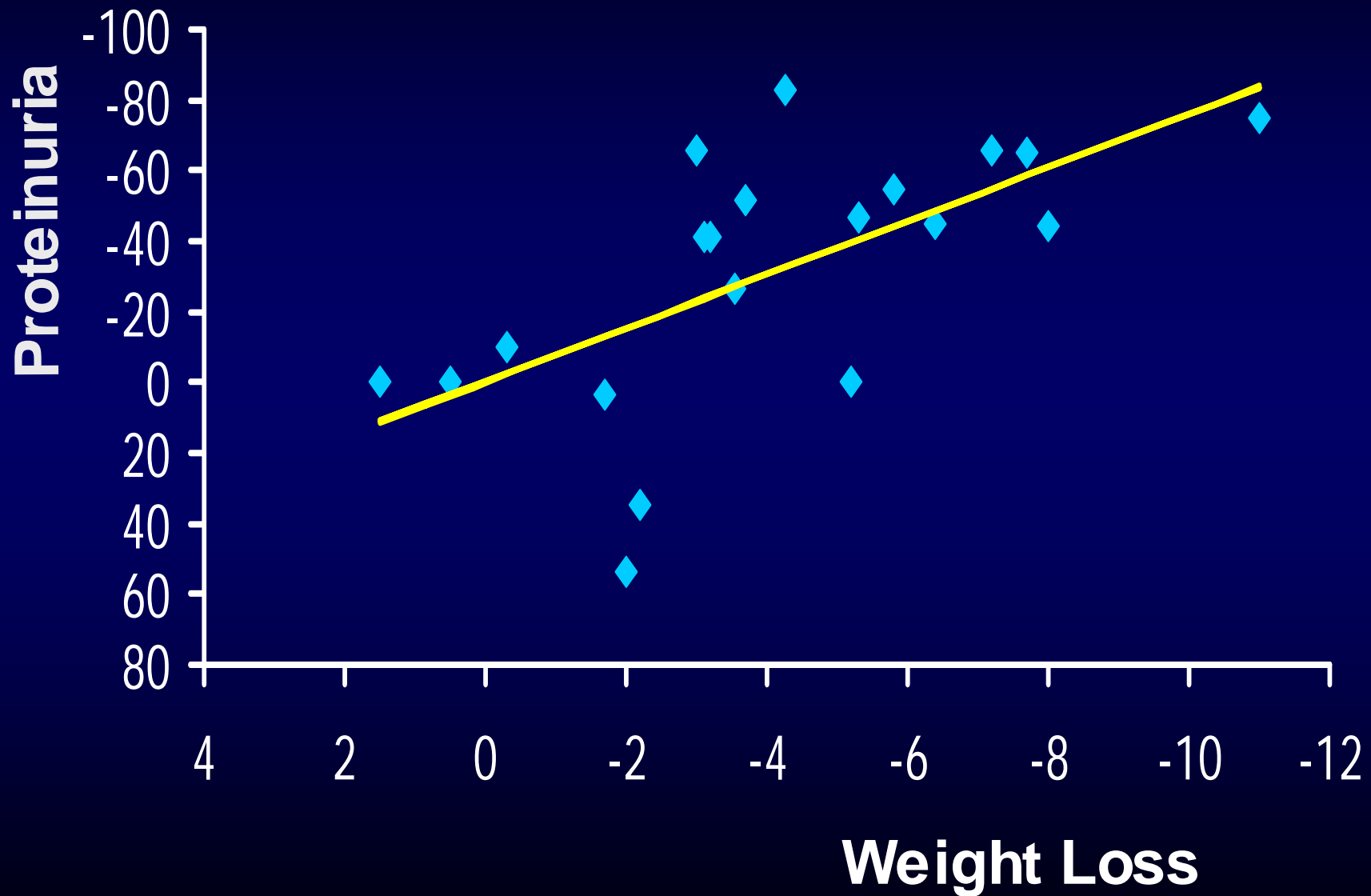
- **Fifteen obese patients (BMI>30 Kg/m²) with FSG**
- **Follow-up 82±57 months (range 36-204)**
- **Seven (46%) patients showed progressive renal insufficiency, 5 of them starting chronic dialysis**
- **Serum creatinine at presentation associated with development of progressive renal failure**



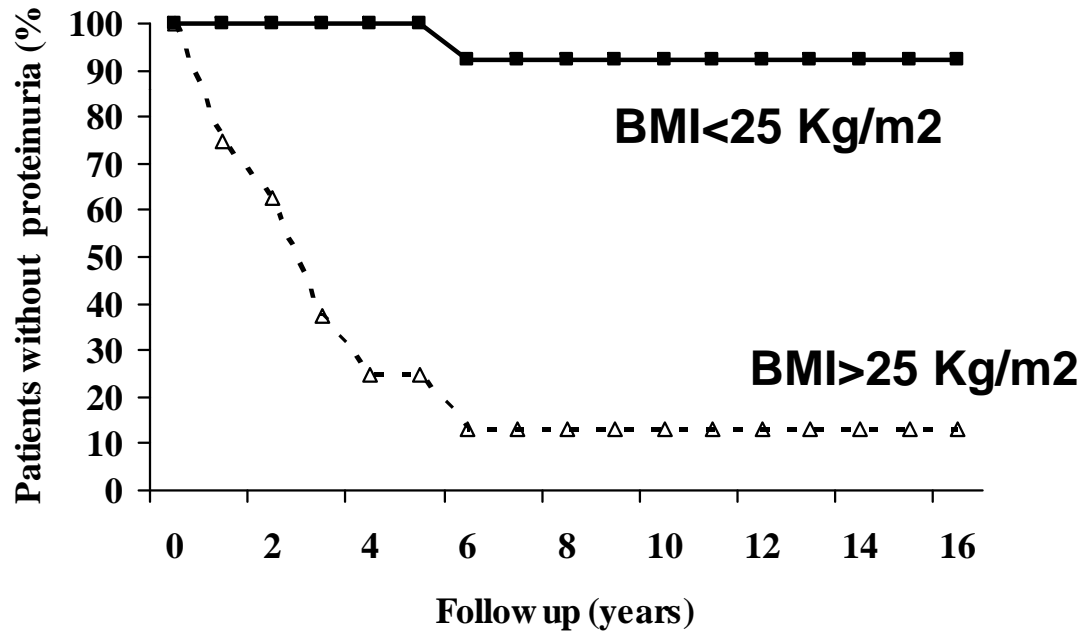


Praga M et al. Nephrol Dial Transplant 2001; 16: 1790-1798

BENEFICIAL EFFECTS OF WEIGHT LOSS IN OVERWEIGHT PATIENTS WITH PROTEINURIC NEPHROPATHIES. Morales E, Valero MA, León M, Hernández E, Praga M. *Am J Kidney Dis* 2003; 41:319-327



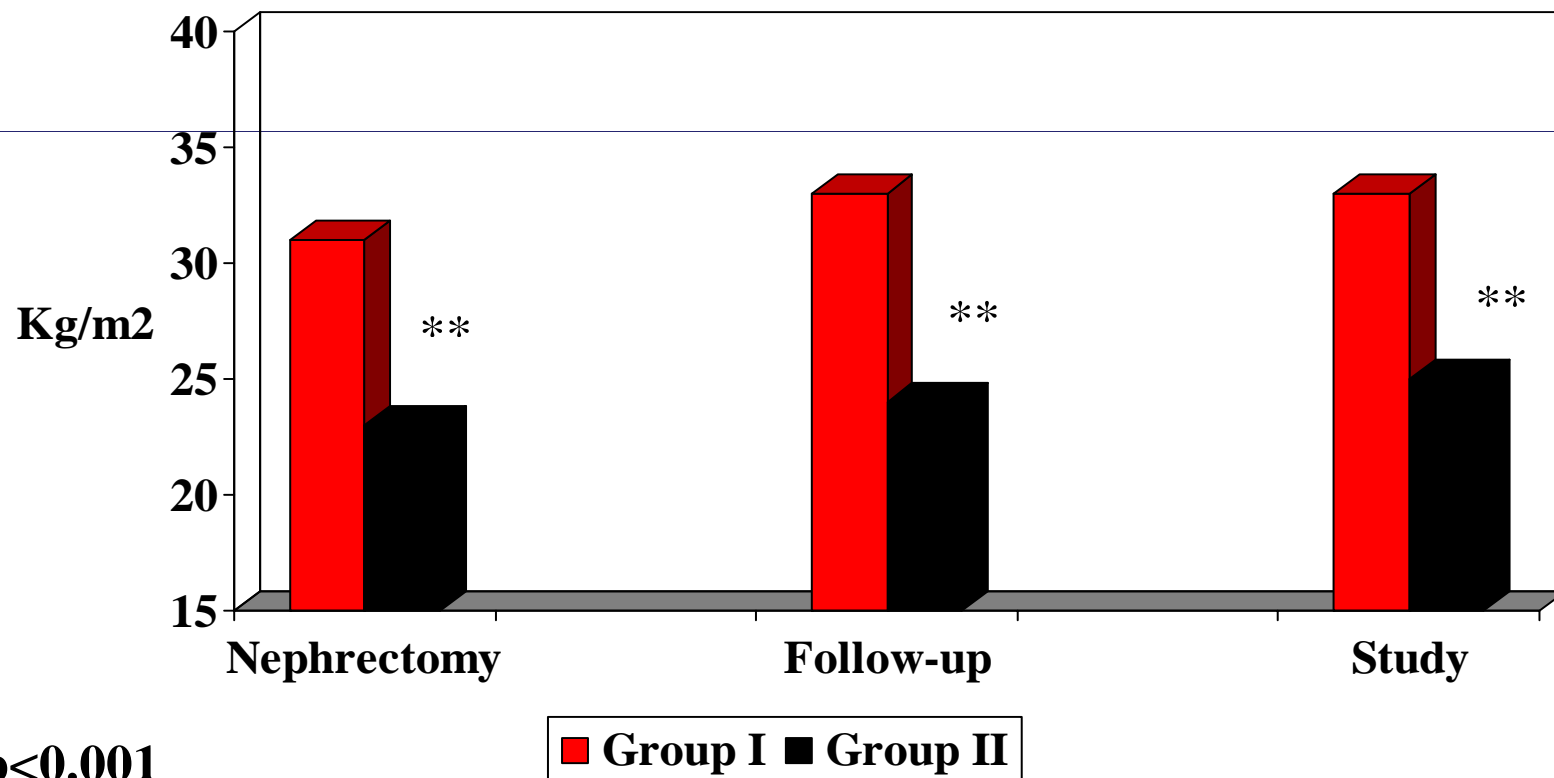
Factors influencing the progression of renal damage in patients with unilateral renal agenesis and remnant kidney. E.González, E. Gutiérrez, E.Morales, E. Hernández, A. Andres, i. Bello, R. Díaz-González, O. Leiva and M. Praga. *Kidney Int* 68:263-70,2005



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.
Praga M et al. *Kidney Int* 2000; 58: 2111-2118

Body Mass Index of Patients with Uninephrectomy



Group I: Patients with hyperfiltration nephropathy
Group II: Patients with normal renal function