

## Epidemiology of glomerular disease in adults: A database review

Venice Chávez Valencia\*, Citlalli Orizaga de La Cruz, Jesús Guillermo Becerra Fuentes, Francisco Fuentes Ramírez, Renato Parra Michel, Yuritomo Aragaki, Isela Márquez Magaña, Héctor Leonardo Pazarin Villaseñor, Martha Arisbeth Villanueva Pérez and Mario Alberto García Cárdenas

Nephrology Department, Regional General Hospital no. 46, Instituto Mexicano del Seguro Social (IMSS), Guadalajara, Jal., Mexico

### Abstract

**Introduction:** Glomerular disease is one of the 10 leading causes of death in Mexico. **Objective:** To determine the frequency of glomerulopathies in Western Mexico, in a secondary care IMSS hospital. **Material and methods:** Retrospective analysis in a hospital center. All native kidney biopsies from patients older than 16 years were reviewed from January 2003 to December 2011, in order to establish clinical features, form of presentation and histopathological report. **Results:** One hundred sixty-three biopsy reports were analyzed; patients' average age was  $32.6 \pm 13.3$  years; 55% were female. Twenty-four percent had systemic arterial hypertension (SAH) and 10% had a family history of chronic renal failure. The most frequent types of primary glomerulonephritis (GN) were focal segmental glomerulosclerosis (FSGS) (47%) and membranous GN (15%). The most common secondary GNs were lupus nephropathy (LN) (14%), amyloidosis (1.2%) and diabetic nephropathy (DN) (4%). **Conclusion:** FSGS is the most common glomerulopathy; a lower percentage of immunoglobulin A nephropathy (IgAN) is observed than that reported worldwide. The information here presented is a contribution to the understanding of the prevalence of glomerulopathy in Western Mexico. (Gac Med Mex. 2014;150:403-8)

**Corresponding author:** Venice Chávez Valencia, drvenicechv@yahoo.com.mx

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## Introduction

Chronic kidney disease (CKD) is a public health problem worldwide. Its incidence and prevalence are increasing<sup>1</sup>, due to demographic changes and to the lack of recognition of the disease at early stages, which results in an increased number of patients being included in renal replacement therapy<sup>2</sup>.

In Mexico, CKD is one of the leading causes of hospital-based care at the national healthcare system public sector, where in addition, nephritis and nephrosis were located in 2008 at the 8<sup>th</sup> place among the leading causes of death in the country<sup>3</sup>.

Glomerulopathies can be classified in different ways, such as describing histopathological findings or their clinical-pathological correlation, with the latter being the most practical, since not only does it consider histological findings, but their relationship with clinical manifestations as well<sup>4</sup>.

Renal disease patients develop pathophysiological disturbances and several clinical manifestations<sup>5</sup>. Therefore, renal histological analysis is the most important diagnostic tool in order to enable for a glomerular disease to be assigned to a specific nosological group<sup>6</sup>.

IgAN is the most common glomerulopathy worldwide<sup>7</sup>; however, there is evidence that FSGS is increasing and it is reported as the most common in the U.S.A. among all ethnic groups<sup>8</sup>. Other authors report membranous nephropathy (MN) as the most common cause of adult-onset nephrotic syndrome (NS)<sup>9</sup>.

### Correspondence:

\*Venice Chávez Valencia

Av. Río Nilo, 3975

Col. Villas del Nilo, C.P. 44824, Guadalajara, Jal.

E-mail: drvenicechv@yahoo.com.mx

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In our area, the most common native kidney glomerulopathies have been previously described, but with conflicting reports<sup>10-12</sup>.

Noteworthy, the group of patients is increasingly younger and, therefore, early diagnosis and treatment have an impact on quality of life and cost containment for the national healthcare system.

Currently, percutaneous renal biopsy (PRB) is essential in the practice of nephrology to establish a specific diagnosis. It allows for classification and treatment to be decided<sup>12,13</sup>, as well as for a prognosis to be established.

It is difficult to establish the exact frequency of glomerulopathies, since they can only be diagnosed histopathologically and, on the other hand, many patients presenting with one of them, do it at a stage when they are no longer subjected to PRB. The quality of the PRB depends on the size of the sample, i.e., the number of glomerules. Generally, the amount of glomerules accepted to be optimal is 10-15, but very frequently, 6-10 glomerules are sufficient, and in some cases even one is enough to establish the diagnosis<sup>14</sup>.

The purpose of this study was to identify the frequency of glomerular diseases at the No. 46 IMSS Regional General Hospital Nephrology Department, a secondary care hospital that takes care of population from the west of the country. The indications for PRB were also analyzed and the results compared with national and international reports.

## Material and methods

This is a descriptive, cross-sectional study of patients who underwent PRB with automated gun over a 9-year period (from January 2003 to December 2011) at the No. 46 IMSS Regional General Hospital.

Patients who underwent native kidney PRB with Bard® Magnum® automated gun equipped with 16 G needles, who had complete clinical and electronic records and who provided informed consent for the performance of the biopsy were included, with an age of 16-80 years, regardless of gender, and with a full report issued by the IMSS Western National Medical Center Department of Pathological Anatomy.

All patients had a viral panel report for HIV, hepatitis B and C, antinuclear antibodies, anti-neutrophil cytoplasmic antibodies and complement (C3 and C4), as well as clotting times and renal ultrasound.

Native kidney PRBs with full interpretation of the sample were included for analysis (samples with more than 7 glomerules, with optical microscopy and immunofluorescence were considered to be adequate). Reports

with insufficient material for diagnosis ( $\leq 6$  glomerules), incomplete records and/or absence of PRB report were excluded.

Additionally, the form of clinical presentation was recorded and the patients were classified in four groups, according to whether their initial presentation was adult-onset NS, nephritic syndrome, glomerular persistent microscopic hematuria (PMH) or persistent sub-nephrotic proteinuria (PSnP). Demographic, biochemical and imaging variables were recorded as well.

## Statistical analysis

Dimensional variables were shown as averages with standard deviations ( $\pm$  SD), and nominal variables, as numbers and percentages. The percentual prevalence of glomerulopathies in native kidneys was determined with the total number of patients over the study period.

Parametric and non-parametric descriptive statistics were used. For continuous variables, average and  $\pm$  SD was employed, and for dichotomous nominal or ordinal variables, the number of cases (n) and percentages (%). Analyses were performed using the statistical pack SPSS, Spanish language version 15.

## Results

During the period of study, 534 PRBs were performed in patients of the Nephrology Department, out of which 291 corresponded to renal graft biopsies and 243 to native kidney biopsies. From the total native PRBs, 80 were excluded (33% of total native kidney PRBs): 55 due to incomplete information (no histological report, reason for biopsy), 24 for having less than 7 glomerules and one for being from a patient with collapsing FSGS secondary to HIV.

From the 55 excluded PRBs due to incomplete information, average age was  $35 \pm 13.8$  years, with FSGS diagnoses in 26.6% of the cases, LN in 20%, MN and minimal change disease (MCD) in 13.3%, inconclusive in 13.3%, and mesangioproliferative GN and amyloidosis in 6.6%.

Of the 24 excluded PRBs due to the number of glomerules, 22 were reported to be FSGS, out of which two were reported as MN.

Finally, 163 reports of biopsies meeting the inclusion criteria were analyzed; average age was  $32.6 \pm 13.3$  years and 55% were female subjects; the remaining demographic variables are shown in table 1.

The most common comorbidities found were SAH (24%) and type 2 diabetes mellitus (T2DM) (4%);

**Table 1. Clinical characteristics of the studied patients**

Variable	Value
Number of patients	163
Gender n (%):	
Male	74 (45)
Female	89 (55)
Age (years)	32.6 ± 13.3
Weight (kg)	67.9 ± 15.7
Height (cm)	166 ± 8
BMI (kg/m <sup>2</sup> )	26 ± 5.7
BSA (m <sup>2</sup> )	1.7 ± 0.2
Hypertensive n (%)	39 (24)
Diabetics (%)	7 (4)
MDRD-4-estimated GFR at the moment of PRB (ml/min/1.73 m <sup>2</sup> BSA)	67.7 ± 32
Creatinine prior to PRB (mg/dl)	1.32 ± 0.72

BMI: Body Mass Index; BSA: Body Surface Area; GFR: Glomerular Filtration Rate; MDRD: Modification of Diet in Renal Disease; PRB: Percutaneous Renal Biopsy.

**Table 2. Most frequent glomerulopathies**

Variable	(%)
FSGS	47.0
Membranous GN	15.0
Nephropathy due to SLE	14.0
IgAN	7.0
Membranoproliferative	6.0
T2DM	4.0
Amyloidosis	1.0
Mesangial GN	3.0
MCD	0.6
Inconclusive	2.0

Table 3 shows the main differences between the 4 most frequent glomerulopathies. Of note, patients in the FSGS group were younger and had more deteriorated renal function.

10% had a family history of CKD (siblings, cousins, uncles/aunts).

The main indications for performing the PRB were adult-onset NS (42%), PSnP (38%), glomerular PMH (11%) and nephritic syndrome (9%). During the diagnostic approach screening, patients with PMH had more than 5 red blood cells (RBCs) per field and 60 to 80% RBC had dysmorphism in fresh urine sediment.

The most common primary GNs were FSGS (47%) and MN (15%). Of the secondary GNs, the most common were LN (14%), amyloidosis (1.2%) and DN (4%). The rest of the observed glomerulopathies are described in table 2.

The 24-h proteinuria average for the patients with nephrotic syndrome was 10.6 ± 6 g/day.

Twenty-three biopsies were reported with LN, most of them class IV (34%) followed by class II (30%), III (17%) and V (17%). A higher predominance of disease was found in females, similarly to reports in the literature.

During the study period, only 7 patients had indications for biopsy due to suspected non-diabetic glomerulopathy; however, only one patient had MN; the rest were reported as DN.

## Discussion

Worldwide, the literature reports IgAN<sup>7,15</sup> and MN as being the most frequent causes of CKD; however, in the present study we found that FSGS is the most common primary glomerulopathy in patients from Western Mexico. This differs from classic literature, but is consistent with recent articles showing evidence that, in the U.S.A., FSGS is increasing as a common cause among all ethnic groups<sup>8,15</sup>, with a prevalence of 2.3% in the year 2000<sup>16</sup> and an increase to 4% in 2011<sup>17</sup>.

Worldwide, since 2003, a change has been shown in glomerulopathies epidemiology: MN and FSGS account for the third part of nephrotic syndrome cases followed by minimum change disease (MCD) and IgAN<sup>18</sup>.

In Latin America, varying frequencies have been reported for glomerulopathies: in Peru, membranoproliferative GN is the most common cause of primary glomerular disease (more than 25% of cases)<sup>19</sup>; FSGS is the most frequent in Colombia and Uruguay (34.8 and 29.3%, respectively)<sup>20,21</sup>; Cuba reports MCD as the most frequent (19.6%) and FSGS is the third cause (11.3%)<sup>22</sup>.

In Mexico, reports regarding the frequency of glomerulopathies have not been homogeneous. Although it has been reported that the most frequently encountered

**Table 3. Main differences between the 4 most frequent glomerulopathies**

Variable	FSGS (n = 77)	MN (n = 24)	LN (n = 23)	IgAN (n = 12)
Age (years)	25.9 ± 10.4	41.5 ± 10.9	32.2 ± 12.3	33.5 ± 13.2
Gender (male:female)	45:32	10:14	3:20	5:7
SAH, n (%)	10 (13)	3 (13)	4 (17)	2 (16)
DM, n (%)	0 (0)	1 (4)	0 (0)	0 (0)
BMI (kg/m <sup>2</sup> BSA)	25 ± 5.1	26.4 ± 5.3	25.7 ± 3.8	27.1 ± 4.7
Hemoglobin (g/dl)	14.6 ± 2.1	12.9 ± 1.3	11.6 ± 2.0	14.6 ± 1.3
Creatinine (mg/dl)	1.5 ± 0.75	1.0 ± 0.6	1.0 ± 0.47	0.8 ± 0.2
Urea (mg/dl)	46.4 ± 17.7	34.6 ± 17	44.8 ± 19.5	26.9 ± 8.8
GFR (ml/min/1.73 m <sup>2</sup> )	62.5 ± 28.6	76.8 ± 34.9	70.5 ± 37.1	87.9 ± 46.1
Cholesterol (mg/dl)	228.9 ± 87.8	316.6 ± 135	208.1 ± 66	168.6 ± 32.5
Triglycerides (mg/dl)	203.5 ± 140.2	343.8 ± 249.2	155.9 ± 60.4	66 ± 19.3
Albumin (g/dl)	3.1 ± 1.1	2.6 ± 1.0	2.4 ± 1.2	3.8 ± 0.9
24-h proteinuria (g)	5.1 ± 6.1	7.9 ± 5.6	5.6 ± 5.4	2.7 ± 3.1
Right kidney dimensions (mm)	94.7 x 47.1	109.6 x 48	110.1 x 44.6	96.6 x 47.5
Left kidney dimensions (mm)	95.4 x 48.8	108.2 x 55	107.5 x 53.3	95.9 x 52.2
Glomerule number in optic microscopy (average)	10.1 ± 4.1	11.6 ± 4.6	11.7 ± 4.7	14.5 ± 8.4
Clinical form of presentation:				
Nephrotic syndrome, n (%)	28 (36)	18 (75)	8 (35)	1 (8)
Nephritic syndrome, n (%)	5 (6)	1 (4)	4 (17)	1 (8)
Sub-nephrotic proteinuria, n (%)	43 (56)	5 (20)	8 (35)	0 (0)
Microscopic hematuria, n (%)	1 (1)	0 (0)	3 (13)	10 (84)

lesions are FSGS (34%) and mesangioproliferative GN (28%)<sup>12</sup>, other national studies report MN (27-34.8%)<sup>10,11</sup>, systemic lupus erythematosus (SLE) (19.6%) and IgAN (10.9%) as the most common histopathologic diagnoses.<sup>11</sup>

Having found in our study that FSGS is the leading cause, we must remember that untreated patients with nephrotic proteinuria and FSGS have a poor prognosis and progress to end-stage renal disease over a 3-6 year period<sup>23</sup>; therefore, they must receive an early treatment in order to impact on the natural course of the disease, improve their quality of life and contain the costs for healthcare institutions.

The reviewed reports show a higher frequency of glomerulopathies in the female sex, as in our study, where 55% were female patients.

It is important highlighting that this population is younger than those in other national and international studies, which report an average age of 36 ± 13 years<sup>15</sup>; this can be partially explained by genetic differences within the population, or even environmental exposure to antigens or agents that might induce the disease, as proposed by the hygiene hypothesis<sup>19</sup>.

These variations within the same country could be correlated with the geographical area and the ethnic groups living there, with their respective genetic differences; however, up to this moment, there is no national registry available that allows for possible geographic-population-based patterns to be determined.

The clinical syndromes found are varied, but the most common is the nephrotic one, which constitutes the main indication for renal biopsy: 42% of the cases, a

figure that is consistent with series where frequency ranges from 30 to 52%<sup>12,21</sup>.

Among the patients subjected to renal biopsy and with criteria for nephrotic syndrome, the most common histopathologic diagnosis is FSGS (36%), which is consistent with recent articles, where an important increase of this disease has been seen as a cause of nephrotic syndrome in the past few years, being currently considered the leading cause of nephrotic syndrome in white adults. This is not true for MN, classically recognized as the main cause of NS in adults, and whose incidence has remained steady over time<sup>15</sup>.

The FSGS frequency found here falls within the mean of what several authors report, whose percentages go from ranges as high as 50-60%<sup>17</sup> to ranges as low as 20-25%<sup>15</sup> in series of adult patients.

In spite of the multiplicity of factors identified in FSGS, approximately 80% of the cases remain as the primary cause<sup>17</sup>, as in our population, if the patient with HIV-associated collapsing FSGS is excluded.

Ultrasound is a decisive factor in our hospital. Prior to performing the PRB, renal length is measured and renal morphology is assessed. We considered renal size under 9 cm to be a contraindication, since previous studies in healthy Mexicans<sup>24</sup> have shown that the renal size mean for males with left renal length (LRL) is  $107.16 \pm 6.97$  mm and with right renal length (RRL),  $105.74 \pm 5.74$  mm, and for women, LRL of  $104.6 \pm 7.96$  mm and RRL of  $102.99 \pm 6.85$  mm. Should we have based our study on Rivera Hernández recommendations<sup>25</sup>, who considers renal size under 10 cm to be a contraindication, approximately half the patients in the present study would have not been subjected to the procedure.

In our series, renal biopsy was practised generally on patients with renal disease already chronic, most evident in FSGS and IgAN carriers, as suggested by creatinine levels above normal values, as well as a small renal size, so far without lethal complications. We should consider that the height mean in this group was  $166 \pm 8$  cm and the group mean for LRL,  $100.09 \pm 19.81$  mm, and for RRL,  $100.19 \pm 18.03$  mm.

Among the secondary GN causes, LN is the most frequent, just as reported by literature over the world<sup>7,12,20</sup>.

Although DN does not occur in 20-40% of DM patients and is the reason to start dialysis<sup>26</sup>, this microangiopathic condition is correlated with diabetic retinopathy and, thus, renal biopsy is usually not necessary in these cases; it is performed in patients with renal function declining more rapidly than expected, active

urine sediment or upon diagnostic suspicion of alternative systemic disease or primary glomerulopathy<sup>26-28</sup>, criteria that are used as part of the screening procedures in our center to perform PRBs.

Among the secondary GN causes found in our study, LN was the most common, and class IV the most frequent histological pattern, as reported by worldwide literature<sup>7,12,20</sup>. Usefulness of the study in patients with secondary nephropathies impacts mainly on their treatment and prognosis.

Several authors have reported on the usefulness of PRB<sup>12-14</sup>, which can be performed safely even at secondary care level.

In different countries of the world and in Latin America there are complete reports on glomerulopathies and their variations in prevalence over time, except in Mexico, where, although several studies on the subject do exist, none includes all ethnic groups and the presented course.

This work might serve to develop, together with different institutions, a national glomerulopathies registry, joining efforts to avoid data duplicity and, most importantly, being Mexico a country of ethnic groups, to know the regional and national epidemiology of each one of them.

In conclusion, in the present study we found that FSGS is the most common glomerulopathy and the main cause of nephrotic syndrome, which is consistent with reports by some Latin American authors. It should be noted that the presentation of this entity is more frequent in the male sex, in young populations and with more deterioration of the renal function; additionally, a lower frequency of IgAN is shown.

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## References

1. National Kidney Foundation. NFK-DOQI: Clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39:S1.
2. McClellan WM, Knight DF, Karp H, Brown WW. Early detection and treatment of renal disease in hospitalized diabetic and hypertensive patients: Important differences between practice and published guidelines. *Am J Kidney Dis.* 1997;29:368.
3. Gómez-Dantés O, Sesma S, Becerril VM, Knaut FM, Arreola H, Frenk J. Sistema de salud de México. *Salud Publica Mex.* 2011;53 Suppl 2:s220-32.
4. Adler Sharon G. An outline of essential topics in glomerular pathophysiology, diagnosis, and treatment for nephrology trainees. *Am J Kidney Dis.* 2003;42(2):395-418.
5. Glasscock RJ. Symptomatic therapy. En: Ponticelli C, Glasscock RJ, eds. *Treatment of primary glomerulonephritis.* 2.<sup>a</sup> ed. Gran Bretaña: Oxford University Press; 2009. p. 1.
6. Glasscock RJ, Cohen AH, Adler Sharon G. Primary glomerular diseases. En: Brenner BM, Rector FC, eds. *The Kidney.* 5.<sup>a</sup> ed. Filadelfia: WB Saunders; 1996. p. 1392-495.

7. Pesce F, Paolo Schena F. Worldwide distribution of glomerular diseases: the role of renal biopsy registries. *Nephrol Dial Transplant.* 2010;25:334-6.
8. Hanco JB, Mullan RN, O'Rourke DM, McNamee PT, Maxwell AP, Courtney AE. The changing pattern of adult primary glomerular disease. *Nephrol Dial Transplant.* 2009;24(10):3050-4.
9. McQuarrie EP, Mackinnon B, Stewart GA, Geddes CC. Scottish Renal Biopsy Registry. Membranous nephropathy remains the commonest primary cause of nephrotic syndrome in a northern European Caucasian population. *Nephrol Dial Transplant.* 2010;25(3):1009-10.
10. Méndez Durán A, Medel Barajas T, Fuentes Luitón E, Pérez Santana ME, Popoca Martínez MC. Frecuencia de glomerulopatías en el Centro Médico Nacional «20 de noviembre». *Rev Esp Med Quir.* 2004;9(2):23-6.
11. Jiménez Bobadilla A, Ávila Casado MC, Gopar Méndez P, Venegas Zarate R, Zaragoza Cruz N, Velásquez Paz A. Perfil epidemiológico de las glomerulopatías. *Rev Eviden Invest Clin.* 2009;2(2):56-61.
12. Mendiola Fernández R, Gómez Vázquez JA, Cardona Pérez MA, Noyola Villalobos HF, Martínez Calva IE. Biopsia renal percutánea, experiencia en el Hospital Central Militar. *Rev Sanid Milit Mex.* 2006;60(6):379-82.
13. Rodríguez Castellanos F, Herrera Acosta J. ¿Es realmente necesaria la biopsia renal en la práctica clínica actual? *Rev Inv Clin.* 2000;52(2):111-2.
14. Amann K, Hass CS. What you should know about the work-up of a renal biopsy. *Nephrol Dial Transplant.* 2006;21:1157-61.
15. Swaminathan S, Leung N, Lager DJ, et al. Changing Incidence of Glomerular Disease in Olmsted County, Minnesota: A 30-Year Renal Biopsy Study. *Clin J Am Soc Nephrol.* 2006;1:483-7.
16. Kitiyakara C, Eggers P, Kopp JB. Twenty-One-Year Trend in ESRD Due to Focal Segmental Glomerulosclerosis in the United States. *Am J Kidney Dis.* 2004;44:815-25.
17. D'Agati VD, Kaskel FJ, Falk RJ. Focal Segmental Glomerulosclerosis. *N Engl J Med.* 2011;365:2398-411.
18. Kodner C. Nephrotic Syndrome in Adults: Diagnosis and Management. *Am Fam Physician.* 2009;80(10):1129-34.
19. Johnson, RJ, Hurtado A, Merszei J, Rodríguez-Iturbide B, Feng L. Hypothesis: Dysregulation of Immunologic Balance Resulting From Hygiene and Socioeconomic Factors May Influence the Epidemiology and Cause of Glomerulonephritis Worldwide. *Am J Kidney Dis.* 2003;42(3):575-81.
20. Arias LF, Henao J, Giraldo RD, Carvajal N, Rodelo J, Arbeláez M. Glomerular Diseases in a Hispanic population: review of a regional renal biopsy database. *Sao Paulo Med J.* 2009;127(3):140-4.
21. Mazzuchi N, Acosta N, Caorsi H, et al. Frecuencia de diagnóstico y de presentación clínica las glomerulopatías en el Uruguay. *Nefrología.* 2005;25(2):113-20.
22. Benítez LLanes O, Fuentes Abreu J, Pérez Bomboust I, Cuervo Cura R, Valdés Salazarte A. Instituto Superior e Medicina Militar «Dr. Luis Díaz Soto». La biopsia renal en el diagnóstico de las glomerulopatías. *Rev Cubana Med.* 2002;4(2):87-92.
23. Chun MJ, Korbert SM, Schwartz MM, Lewis EJ. Focal Segmental Glomerulosclerosis in Nephrotic Adults: Presentation, Prognosis, and Response to Therapy of the Histologic Variants. *J Am Soc Nephrol.* 2004;15:2169-77.
24. Oyuela Carrasco J, Rodríguez Castellanos F, Kimura E, Delgado Hernández R, Herrera-Felix JP. Longitud renal por ultrasonografía en población mexicana adulta. *Nefrología.* 2009;29(1):30-4.
25. Rivera Hernández F. Biopsia renal. *NefroPlus.* 2009;2(1):1-8.
26. American Diabetes Association. Standards of Medical Care in Diabetes 2013. *Diabetes Care.* 2013;36(Suppl. 1):S11-66.
27. Adler SG, Salant DJ. An Outline of Essential Topics in Glomerular Pathophysiology, Diagnosis, and Treatment for Nephrology Trainees. *Am J Kidney Dis.* 2003;42(2):395-418.
28. Gross JL, De Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic Nephropathy: Diagnosis, Prevention, and Treatment. *Diabetes Care.* 2005;28:164-76.