ORIGINAL ARTICLE

JNEPHROL 2007; 20: 329-335

www.sin-italy.org/jnonline – www.jnephrol.com

The Pisa experience of renal biopsies, 1977-2005

Vincenzo Panichi, Antonio Pasquariello, Maurizio Innocenti, Mario Meola, Emanuela Mantuano, Sara Beati, Sabrina Paoletti, Cristina Consani, Rodolfo Puccini, Leonardo Casarosa, Vittorio Gattai, Cristina Filippi, Luigi Moriconi, Giuliano Barsotti, Paolo Rindi, Roberto Palla

Internal Medicine Department and Renal Unit, Hospital of Pisa, Pisa - Italy

ABSTRACT

Introduction: **Although several registries collecting data of patients with kidney diseases exist, only a few specifically collect data relating to renal biopsy. Kidney biopsy has been performed routinely in Pisa since 1977; the aim of this study was to report the relative frequency of nephropathies according to gender, age at time of biopsy, clinical presentation and renal function, based on histological diagnoses during the years 1977 through 2005. During this time, 3,810 kidney biopsies were performed, of which 89.3% were from native (n=3,446) and 10.7% from transplant kidneys. Throughout this period, 5% of renal biopsies were not diagnostic, so in this paper we report data regarding 3,269 native kidney nephropathies.**

Methods: **During the years 1977 through 2005, data for renal biopsies were collected on specific registers filled out by clinicians. Information collected in the database included a variety of indicators, such as clinical anamnesis, creatinine clearance, daily proteinuria, hemoglobin levels, blood pressure, height and weight, clinical presentation, and current medications. Clinical presentation was defined as urinary abnormalities (UA), nephrotic syndrome (NS) and acute nephritic syndrome (ANS). Renal diseases were divided into 4 major categories: primary glomerulonephritis (GN), secondary GN, tubulointerstitial nephropathies (TIN) and vascular nephropathies (VN).**

Results: **From 1977 up to 1987, a mean of 95 ± 18 renal biopsies/year were performed; this number significantly increased to 185 ± 22 renal biopsies/year (range 138-200) ($p<0.001$) in the following period (1988-2005). Renal biopsy was more frequently performed in males (59%) compared with females (41%). Of all diseases of the native kidney, primary GN was the most frequent (66%), followed by secondary GN (25.6%), TIN (4.2%) and VN (4.2%). The type of primary GN with the highest frequency was mesangial GN (both IgA and non-IgA) (45.7%), followed by membranous GN (23%), focal segmental glomerulosclerosis (19.8%), minimal change disease (5.3%), crescentic GN (4.2%) and postinfectious GN (2%). In terms of age, renal biopsy was more frequently performed in patients aged 20 to 60 years, and nearly 60% of patients presented a glomerular filtration rate (GFR) >60 ml/min at the time of biopsy. The main clinical reason for performing renal biopsy was UA, in all the types of nephropathies.**

Conclusions: **We confirm data that renal diseases are more frequent in men, with the exception of secondary GN. The mean age at diagnosis was 42 years resulting from the tendency not to perform renal biopsies in children and in elderly patients. Renal biopsy was mainly performed in patients with GFR >60 ml/min and asymptomatic urinary abnormalities suggesting concern on the part of clinicians regarding glomerular diseases. The tendency to perform renal biopsies has been significantly increasing throughout our follow-up period.**

Key words: *Renal biopsy, Glomerulonephritis*

Introduction

Clinical epidemiological research is the key feature of the development of good quality medicine treatment. Although there are several registries collecting data from patients with kidney disease, only a few specifically collect data relating to renal biopsy. One such registry is the Italian Registry of Renal Biopsies (IRRB) which since 1987 has collected all data (age, gender, clinical presentation, renal function and histological diagnosis) regarding biopsies performed in Italy (1). There are several epidemiological population-based studies of biopsy-proven nephropathies with detailed clinical-pathological correlations that may different according to the country or region analyzed (2-8). The Hospital of Pisa was one of first to introduce renal biopsy in Italy: kidney biopsy has routinely been performed in Pisa since 1977. Since 1977 and up to December 2005, the 2 renal units in Pisa performed 3,446 biopsies from native and 364 biopsies from transplant kidneys. Throughout this period, 5% of renal biopsies were not diagnostic, so in this paper we report data regarding 3,269 native kidney nephropathies.

The aim of this paper is to report the relative frequency of native kidney nephropathies in our registry according to gender, age at time of biopsy, clinical presentation and renal function, based on the histological diagnosis, and to identify the most frequent clinical syndromes and the manifestations of each renal disease.

Study population and methods

In Pisa, 3,810 renal biopsies were performed during the years 1977 through 2005, by its 2 renal units (the University Nephrology Unit and the Nephrology and Dialysis Gabriele Monasterio Unit) of which 89.3% were from native and 10.7% from transplant kidneys. We here evaluated data regarding the 3,269 diagnostic native kidney biopsies.

These data were collected on specific registers filled out by clinicians. Information collected in the database included a variety of indicators, such as clinical anamnesis, creatinine clearance, daily proteinuria, hemoglobin levels, blood pressure, height and weight (when available), clinical presentation and current medications. This clinical information is more complete in the registers collected from 1987 through 2005, compared with the data relative to the previous 10 years (from 1977 to 1987) which report only the histological diagnosis, personal data and limited clinical information. Nephrotic syndrome (NS) was defined as proteinuria greater than 3.5 g/day per 1.73 m^2 and serum albumin less than 2.5 g/dL. Acute nephritic syndrome (ANS) was defined as hematuria, hypertension, oliguria, edema and reduced glomerular filtration rate (GFR). Urinary abnormalities (UA) included persistent nonnephrotic proteinuria and/or microscopic hematuria. Hypertension was considered when blood pressure was higher than 140/90 mm Hg. Acute renal failure (ARF) was defined as a rapid deterioration of GFR. GFR was calculated according to the Modification of Diet in Renal Disease (MDRD) formula.

Renal diseases, in accordance with the Italian Register of Renal Biopsies (IRRB), were divided into 4 major categories: primary glomerulonephritis (GN), secondary GN, tubulointerstitial nephropathies (TIN) and vascular nephropathies (VN).

We have considered primary GN (group 1) to include minimal change disease, mesangial GN (IgA, non-IgA mesangial nephropathy and Schönlein-Henoch syndrome), membranous GN, focal segmental glomerulosclerosis (FSGS), membranoproliferative GN (MPGN), crescentic GN and postinfection GN.

Secondary GN (group 2) includes a large group of diseases: immune-mediated GN (systemic lupus erythematosus, necrotizing vasculitis), metabolic and hereditary disorder–associated GN (amyloidosis, diabetes mellitus, Alport's syndrome, Fabry's disease and other hereditary disorders), dysgammaglobulinemia-associated GN (essential mixed cryoglobulinemia, Waldenström's macroglobulinemia, monoclonal gammopathy, multiple myeloma-associated renal disease and light chain disease).

Tubulointerstitial nephropathies (TIN) (group 3) include chronic TIN, acute TIN, acute tubular necrosis and chronic pyelonephritis.

Benign nephroangiosclerosis, thrombotic microangiopathy, malignant nephroangiosclerosis, cortical necrosis, preeclampsia acute ischemic damage, pre-acute renal insufficiency and renal vessel thrombosis were classified as vascular nephropathies (VN) (group 4). Into this group we have also placed the few cases (2) of loin pain-hematuria syndrome.

Data regarding 5% of all biopsies, which could not be adequately classified due to inadequate sampling, normal renal tissue or end-stage renal disease, were not included in our analysis.

Statistical analysis

Each year, data were stored in a database file (Microsoft

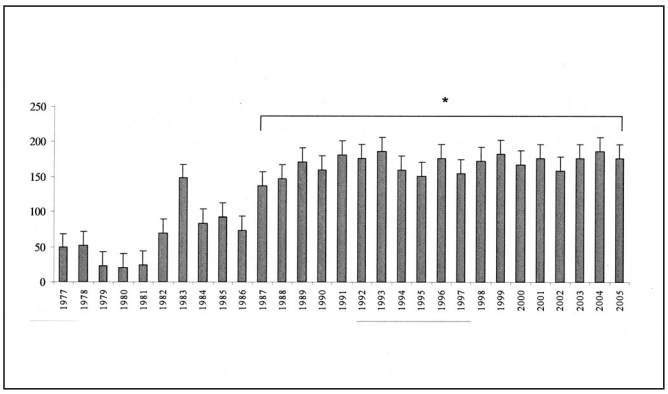

Fig. 1 - Number of kidney biopsies each year, 1977-2005.

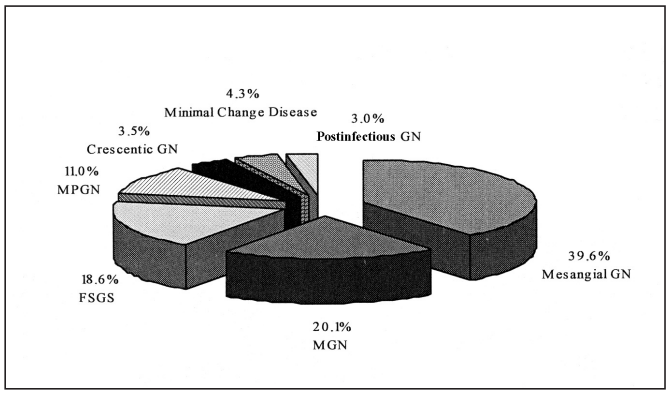

Fig. 2 - Frequency of histological diagnosis of primary glomerulonephritides. FSGS = focal segmental glomerulosclerosis; GN = glomerulonephritis; MPGN = membranoproliferative GN.

Access 2000). All statistical analysis was performed using the statistical package SPSS for Windows version 10.0.6 (SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution with the Kolmogorov-Smirnov test. The values are expressed as medians when the parameters did not fit into a normal (Gaussian) distribution. The chi-square test and Fisher's test were used to compare qualitative variables. A p value of less than 0.05 (by 2-tailed test) was considered to indicate statistical significance.

RESULTS

From 1977 up to 1987, a mean of 95 ± 18 renal biopsies/year were performed; this number significantly increased, roughly tripling, to 185 ± 22 renal biopsies/year (range 138-200) ($p<0.001$) in the following period (1988-2005) (Fig. 1). Together the 2 Pisa nephrology units performed 3,446 biopsies from native kidneys (90.6%) and 364 biopsies from transplant kidneys (9.4%) in a period of 28 years. We report here data regarding 3,269 diagnostic renal biopsies.

Of all diseases of native kidney, primary GN was the most frequent (71.6%), followed by secondary GN (18.4%), TIN (5.7%) and VN (4.3%).

The type of primary GN with the highest frequency was mesangial GN (39.6%), followed by membranous GN (20.1%), FSGS (18.6%), MPGN (11%), crescentic GN (4.3%), minimal change disease (3.5%) and postinfectious GN (3%) (Fig. 2).

Primary GN was more frequent in males (64.4%) compared with females (35.6%); this was also true for TIN

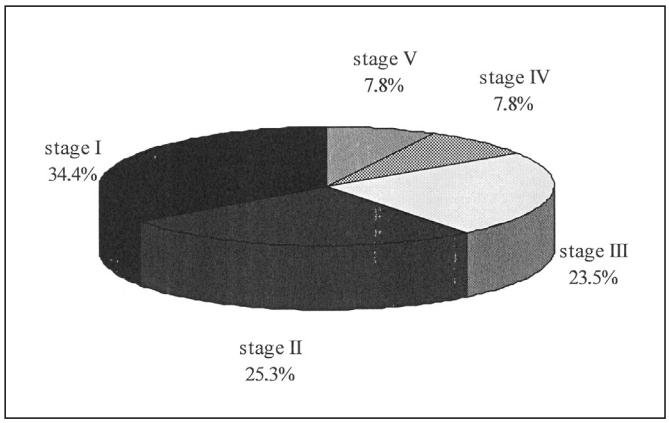

Fig. 3 - Renal function at time of biopsy: percentages of patients undergoing a renal biopsy who had different stages of chronic kidney disease (CKD). GFR was calculated according to the MDRD formula, and stages of CKD were classified according to K/DOQI guidelines.

(males 64%, females 36%) and for VN (males 65%, females 35%). In contrast, secondary GN was more frequent in females (61.2% female vs. 38.8% males). The diseases with a higher frequency in males were mesangial GN (67.5% males, 32.5% females). By contrast, as is well-known, the more common disease in females are the immunomediated GNs, in particular systemic lupus erythematosus (89.7% females vs. 10.3% males).

In terms of age, biopsies were more frequently performed in patients aged 20-60 years. Primary GNs were found in patients 41.52 ± 1.92 years old, secondary GN in patients 47.2 ± 3.7 years old, TIN in those 46.23 ± 1.73 years old and VN in those 49.28 ± 2.59 years old ($p<0.05$ for group 1, vs. groups 2-4).

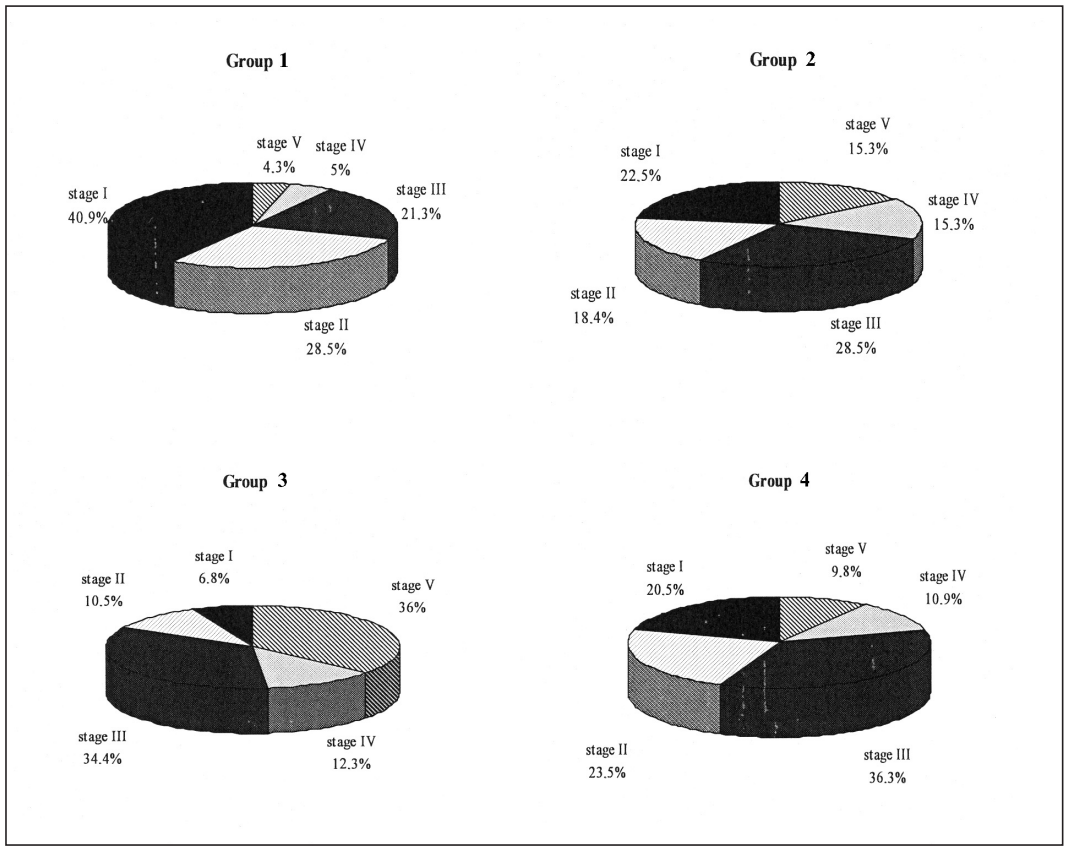

Fig. 4 - Renal function at time of biopsy in 4 groups of renal biopsy patients classified by nephropathy: group 1 = primary glomerulonephritis (GN); group 2 = secondary GN; group 3 = tubulointerstitial nephropathies (TIN); and group 4 = vascular nephropathies (VN). GFR was calculated according to the MDRD formula, and stages of CKD were classified according to K/DOQI guidelines.

The great majority (59.7%) of patients underwent a renal biopsy with a GFR >60 ml/min (stage I-II chronic kidney disease [CKD]; Kidney Disease Outcomes Quality Initiative [K/DOQI] guidelines) with 15.6% in stage IV-V, K/DOQI (Fig. 3). When patients were divided into groups according to renal pathology, a large percentage of patients affected by TIN (group 3) and secondary GN (group 2) showed a reduced GFR at the time of biopsy (Fig. 4).

Urinary abnormalities were the main indications to perform a renal biopsy in all the different biopsied nephropathies: 63% of cases of primary GN, 58% of cases of secondary GN, 79% cases of TIN and 72% of cases of VN. The class of nephropathy that most frequently presented with NS was secondary GN (39%) followed by primary GN (30%) (Fig. 5).

The percentage of patients from outside the region of Tuscany who received renal biopsies in the different periods of observation was also investigated. The means of 3 different periods were compared: namely 1980-1982 vs. 1990-1992, and vs. 2000-2002. The percentage of patients from outside Tuscany who were biopsied in Pisa decreased from 41.6% ± 4% (1980-1982) to 37% ± 5% (1990-1992) and 33.4% ± 3.7 % in the final period (2000-2002).

The percentages of cases of IgA nephropathy (IgAN) and of FSGS diagnosis with respect to the total number of cases of primary GN throughout the years recorded are shown in Figures 6 and 7.

Discussion

This article reports on a 28-year retrospective epidemiological study of native kidney biopsies performed in the Hospital of Pisa since 1977. The practice of renal biopsy has been increasing during the last few decades; from 1977 to 1987, a mean of 95 ± 18 renal biopsies/year were performed. This number significantly increased to 185 ± 22 renal biopsies/year (range 138-200) ($p<0.001$) in the following period (1988 to 2005). In Italy as a whole, about 99 renal biopsies/million persons per year are actually performed (9-11). In Tuscany, this procedure was first introduced by Prof. Quirino Maggiore in the late 1970s and is still performed more frequently than in other Italian regions

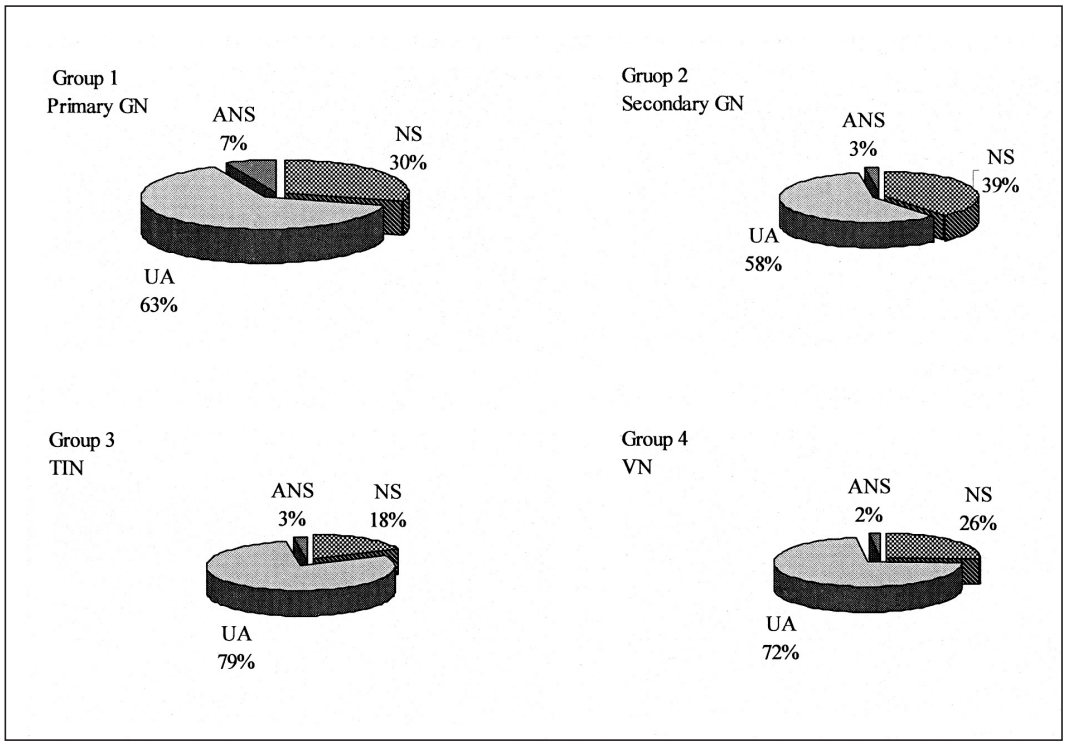

Fig. 5 - Clinical presentation at the time of biopsy according to the type of nephropathy. Nephrotic syndrome (NS), urinary abnormalities (UA) and acute nephritic syndrome (ANS).

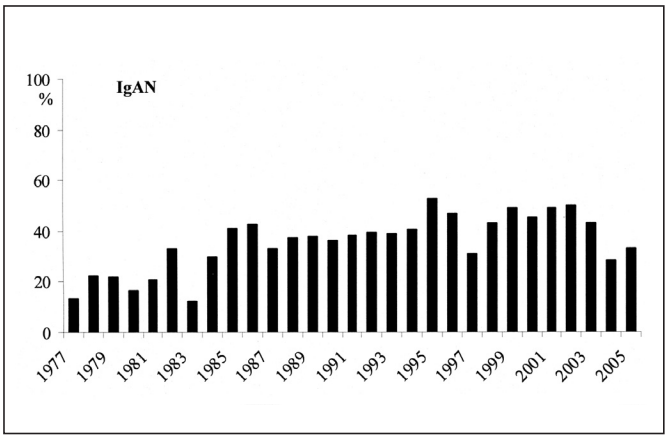

Fig. 6 - The percentage of cases of IgA nephropathy (IgAN) diagnosed in the total number of cases of primary glomerulonephritis recorded for 1977-2005.

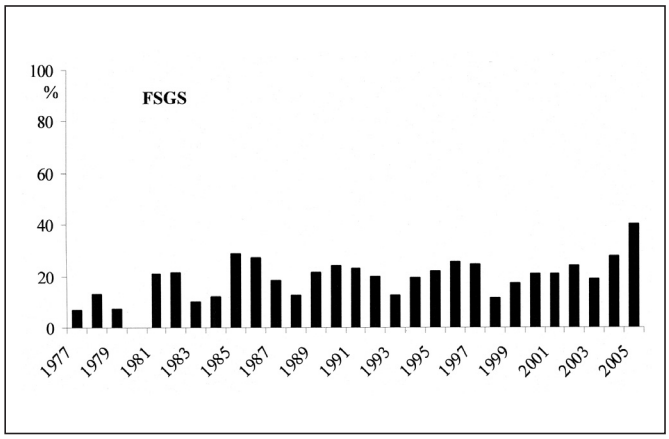

Fig. 7 - The percentage of cases of focal segmental glomerulosclerosis (FSGS) diagnosed in the total number of primary glomerulonephritis cases recorded for 1977-2005.

(about 166 biopsies/million persons per year). In particular, from 1987 to 2005 about 185 renal biopsies/year were evaluated in Pisa – a geographical area with a population of roughly 0.2 million persons, a frequency of renal biopsies per person that is greatly above the Italian and regional average. This is due to the fact that data from all kidney biopsies performed in northwest Tuscany are collected for diagnosis by the nephrology units of Pisa; furthermore, Pisa is still receiving a large number of patients suffering from renal disease, from other regions of Italy. The percentage of patients from outside the region of Tuscany who received a renal biopsy decreased throughout the study period, but it is still very high – over 30% of the total number.

According to data from other registers, we can confirm that kidney biopsies have been more frequently performed

for the diagnosis of primary GN compared with secondary GN, TIN and VN (Fig. 2.). A male predominance of the main clinical syndromes has been observed in the whole population, as occurs in the majority of renal pathologies undergoing kidney biopsy (1). Furthermore, primary GN, TIN and VN are more frequent in men – in particular, mesangial GN and both IgA and non-IgA GN. The higher relative frequency of secondary GN in women may be due to the higher frequency of immune-mediated disease in this gender. In particular, in this group of patients, renal biopsy was mainly performed in systemic lupus erythematosus.

In our study, we found that all categories of renal disease occur mainly in patients aged 20-60 years. This can be explained by the choice to perform an invasive procedure like biopsy principally in patients with a long life expectancy and in the case of in children, only in those with persistent disease who present with major symptoms. As expected, the oldest patients are in group 4 (VN) with a mean age at the time of diagnosis of 49.2 ± 2.5, versus 41.52 ± 1.92 years ($p<0.05$) in patients affected by primary GN.

Urinary abnormalities were the main indications to perform a renal biopsy in our registry, in accordance with the national Italian registry of renal biopsy (1), and in contrast to other registers where nephrotic syndrome is the main indication for kidney biopsy (12). Furthermore, we note that in our database, urinary abnormalities are a more frequent reason for performing a renal biopsy even compared with the data of Gesualdo and colleagues from the Italian registry (1).

Moreover, the great majority (59.7%) of patients were submitted to renal biopsy with a GFR >60 ml/min (stage I-II CKD; K/DOQI) with 15.6% in stage IV-V, K/DOQI (Fig. 4). When patients were divided into groups according to renal pathology, a large percentage of patients affected by TIN (group 3) and secondary GN (group 2) showed a reduced GFR at the time of biopsy (Fig. 5).

As in other European countries, we have not observed any increase in the annual incidence of FSGS as a cause of nephrotic syndrome, as has been shown in other reports, mainly from the United States and Singapore (13, 14). In fact, 3 studies in the United States have disclosed that since 1995, FSGS is the most common cause of adult nephrotic syndrome (14, 15). Moreover, racial differences, nutritional behaviors and environmental factors may have been implicated in this difference in our population.

As was expected, IgAN is the most common primary GN during the whole study period in the general population of the area. The new information furnished by this epidemiological study is that the risk of occurrence of IgAN has become similar in the population living in our region, whatever the age group, during the last period studied. The mean age of patients undergoing renal biopsy progressively increased during the study period, and the policy of referring for renal biopsy was expanded more and more in the elderly as the consequence of the increase in average lifetime. Thus, the incidence of IgAN not only remained similar throughout the period under study, but also became similar in each age group during the last period studied. The stability of the annual incidence of IgAN diagnosis and of end-stage renal disease due to IgAN during this 27-year prospective study strongly suggests that immunogenetic factors could be more important than environmental factors in the onset of IgAN (7, 8).

In conclusion, our study gives further epidemiological information on the evolution of native kidney nephropathy incidence in every age group of a general population during a long observation period of 27 years. We believe that the collection of data on renal biopsies is a useful tool for nephrologists and the availability of this data will help epidemiological studies in health care to answer the several open questions regarding both prevention and treatment of renal disease.

Address for correspondence:
Vincenzo Panichi, MD
Dipartimento Medicina Interna
Via Roma 67
I-56100 Pisa, Italy
vpanichi@med.unipi.it

REFERENCES

1. Gesualdo L, Di Palma AM, Morrone LF, Strippoli GF, Schena FP. The Italian experience of the national registry of renal biopsies. Kidney Int 2004; 66: 890-4.
2. Sung NS, Crowley W Jr, Genel M, Salber P, Sandy L, Sherwood L, Johnson SB, Catanese V, Tilson H, Getz K, Larson E, Scheinberg D, Reece EA, Slavkin H, Dobs A, Grebb J, Martinez R, Korn A, Rimoin D. Central challenges facing the national clinical research enterprise. JAMA 2003; 289: 1278-87.
3. Registro Espanol de Glomerulonefritis: evolution de la frecuencia de las glomerulonefritis primarias y secundarias en Espana en los anos 1991 y 1992. Nefrologia 1994; 14: 288-96.
4. Registro Espanol de Glomerulonefritis: epidemiologia de las glomerulonefritis en Espana: resultadas de 1993. Nefrologia 1995; 15: 435-44.
5. Rivera F, Lopez-Gomez JM, Perez-Garcia R. Spanish Registry of Glomerulonephritis: frequency of renal pathology in Spain 1994-1999. Nephrol Dial Transplant 2002; 17: 1594-602.
6. Davidson AM. The United Kingdom Medical Research Council's Glomerulonephritis Registry. Contrib Nephrol 1985; 48: 24-35.
7. Johnston PA, Brown JS, Braumholtz DA, Davison AM. Clinicopathological correlations and long-term follow up of 253 United Kingdom patients with IgA nephropathy: a report from the MRC Glomerulonephritis Registry. Q J Med 1992; 84: 619-27.
8. Heaf J, Lokkegaard H, Larsen S. The epidemiology and prognosis of glomerulonephritis in Denmark, 1985-1997. Nephrol Dial Transplant 1999; 14: 1889-97.
9. Manno C, Giancaspro V, Schena FP; Gruppo di Immunopatologia Renale della Societa Italiana di Nefrologia. Rapporto finale sul Registro Italiano delle Biopsie Renali (anni 1987-1995). G Ital Nefrol 1998; 15: 281-90.
10. Gruppo di Immunopatologia Renale della Societa Italiana di Nefrologia. Rapporto sul Registro Nazionale delle biopsie renali (anni 1989-1990). G Ital Nefrol 1993; 10: 235-41.
11. Schena FP; the Italian Group of Renal Immunopathology. Survey of the Italian Registry of Renal Biopsies: frequency of the renal diseases for seven consecutive years. Nephrol Dial Transplant 1997; 12: 418-26.
12. Rivera F, Lopez-Gomez JM, Perez-Garcia R. Representation of the Spanish Registry of Glomerulonephritis: frequency of renal pathology in Spain for 1994-1999. Nephrol Dial Transplant 2002; 17: 1594-602.
13. Korbet SM, Genchi RM, Borok RZ, Schwartz MM. The racial prevalence of glomerular lesions in nephrotic adults. Am J Kidney Dis 1996; 27: 647-51.
14 Woo KT, Chiang GS, Pall A, Tan PH, Lau YK, Chin YM. The changing pattern of glomerulonephritis in Singapore over the past two decades. Clin Nephrol 1999; 52: 96-102.
15. Braden GL, Mulhern JG, O'Shea MH, Nash SV, Ucci AA Jr, Germain MJ. Changing incidence of glomerular diseases in adults. Am J Kidney Dis 2000; 35: 878-83.

Received: June 07, 2006
Revised: October 23, 2006
Accepted: February 01, 2007