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Received for publication: 18.12.08; Accepted in revised form: 3.2.09

Nephrol Dial Transplant (2009) 24: 2406–2410

doi: 10.1093/ndt/gfp091

Advance Access publication 4 March 2009

Changing prevalence of glomerular diseases in Korean adults: a review of 20 years of experience

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Abstract

Background. The prevalence of glomerular diseases differs according to geographic area, race, age and indications for a renal biopsy. This study was conducted to evaluate the distribution and changing patterns of renal diseases during the past 20 years in a large patient population in Korea.

Methods. Patients aged 16 years or older who underwent a renal biopsy at Severance Hospital in the Yonsei University Health System from 1987 to 2006 were enrolled. All medical records were reviewed retrospectively.

Results. In total, 1818 patients (M:F = 1.02:1) were reviewed. Glomerulonephritis (GN) comprised 85.9% of the total biopsied cases. The most common primary GN was IgA nephropathy (IgAN) (28.3%), which was followed by minimal change disease (MCD) (15.5%), membranous nephropathy (MN) (12.3%), focal segmental glomerulosclerosis (FSGS) (5.6%) and membranoproliferative GN (MPGN) (4.0%). The most common secondary GN was

lupus nephritis (8.7%). The most common idiopathic nephrotic syndrome was MCD (38.5%), which was followed by MN and IgAN. Among 128 (7.4%) patients who were HBsAg-positive, MN (30.5%) and MPGN (21.1%) were the most common GN. When the incidence rates between 1987–91 and 2002–06 were compared, IgAN increased from 25.6 to 34.5%, while MCD (from 23.2 to 7.0%) and MPGN (from 6.7 to 1.7%) decreased significantly ($P < 0.01$).

Conclusions. IgAN was the most common primary GN, and MCD was the most common cause of nephrotic syndrome. In the 5-year quartile comparison, the relative frequency of IgAN increased, while the relative frequency of MCD and MPGN decreased significantly during the past 20 years.

Keywords: adult; glomerulonephritis; nephrotic syndrome; prevalence; renal biopsy

Introduction

The information obtained from a renal biopsy is critical for identifying a specific diagnosis, reflecting the level of disease activity and allowing informed decisions about treatment to be given. The advent of ultrasonography has made the renal biopsy easier and safer compared to that in the presonography era [1,2].

The prevalence of glomerulonephritis (GN) is different according to the period, geographic area, race, age and indication for a renal biopsy, and recent studies have shown a changing pattern of GN. Previous studies showed that membranous nephropathy (MN) was the most common cause of adult nephrotic syndrome in the United States and Europe. However, recent studies have shown that the frequency of focal segmental glomerulosclerosis (FSGS) is increasing significantly, and FSGS has become the most common GN in black and Hispanic populations [3]. Other studies have shown that IgA nephropathy (IgAN) is the most common cause of GN in white adults [4].

The epidemiology of biopsy-confirmed renal disease provides useful information about the prevalence of renal disease and its clinical manifestations. The epidemiology of GN follows racial and geographical distributions that are influenced by a higher overall prevalence of infectious diseases and differences in social and economic statuses [5,6]. Little information exists on the causes underlying this change, and most of the studies have originated in Western countries.

Koreans have a relatively homogenous ethnicity, and rapid urbanization in Korea is expected to result in changing patterns of glomerular diseases. This study was carried out to evaluate the distribution and changing patterns of renal diseases during the past 20 years in a large-scale patient population in Korea.

Patients and methods

The records of adult patients who underwent a renal biopsy at Severance Hospital in the Yonsei University Health System, Seoul, Korea, from January 1987 to December 2006 were retrospectively reviewed. Indications for a renal biopsy were nephrotic syndrome, acute and chronic renal failure, nephritic syndrome and asymptomatic urinary abnormalities. While for secondary GN, heavy proteinuria and elevated serum creatinine levels were the main indications. There was no significant change in biopsy policy during the study period.

Patients younger than 15 years old were excluded. Incomplete records, inadequate biopsies and the second biopsy in re-biopsy patients were excluded from analysis. The data collected included the date of the renal biopsy, age, sex, level of proteinuria and underlying conditions associated with renal disease.

All biopsies were analysed over four 5-year intervals: 1987–91, 1992–96, 1997–2001 and 2002–06. Primary GN was classified into six groups: minimal change disease (MCD), MN, FSGS, membranoproliferative GN (MPGN), IgAN and other. Secondary GN was classified into four groups: systemic lupus erythematosus, diabetes mellitus, Henoch–Schönlein purpura and other. Nephrotic syndrome was defined as proteinuria >3.5 g/day/1.73 m² and serum albumin <2.5 g/dL.

All the biopsy specimens were prepared and examined by the same group of clinicians, pathologists and technicians. A renal biopsy was processed for light and immunofluorescent microscopy in all submitted cases. Electron microscopy was performed in selected cases, in which diagnosis was not definite by light and immunofluorescent microscopy. The final diagnosis was made for each patient on the basis of both clinical and histologic investigations.

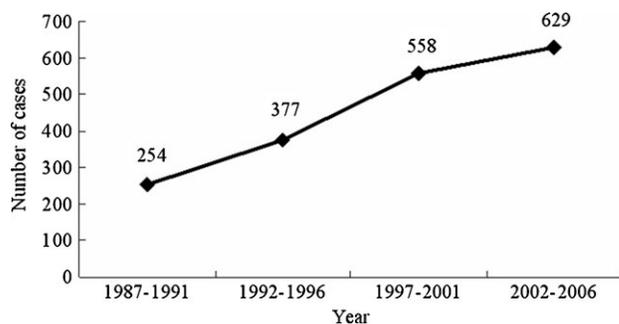


Fig. 1. Cases of renal biopsies.

Table 1. Distribution of a renal biopsy

	Total (n = 1818)	Male	Female
Primary	1346 (74.0%)		
glomerulonephritis			
IgA nephropathy	514 (28.3%)	245	269
Minimal change disease	282 (15.5%)	178	104
Membranous nephropathy	223 (12.3%)	137	86
Focal segmental glomerulosclerosis	101 (5.6%)	55	46
Membranoproliferative glomerulonephritis	72 (4.0%)	51	21
Other	154 (8.5%)	70	84
Secondary	215 (11.8%)		
glomerulonephritis			
Systemic lupus erythematosus	159 (8.7%)	16	143
Diabetes mellitus	36 (2.0%)	19	17
Henoch–Schönlein purpura	18 (1.0%)	12	6
Other	2 (0.1%)	0	2
Normal or minor change	141 (7.8%)	82	59
Others	116 (6.4%)	55	61

The results are reported as the mean or percent. The distribution of patients with varying renal biopsy diagnoses between the 5-year intervals was calculated using Pearson's chi-square analysis. $P < 0.05$ was considered significant.

Results

In total, 1818 patients were reviewed. The average age of the patients at the time of biopsy was 36 years and ranged from 16 to 82 years. The male-to-female ratio was 1.02:1. The mean serum creatinine levels were 1.38 ± 1.3 mg/dL. The patients with massive proteinuria (>3.5 g/day) or proteinuria (0.15–3.5 g/day) were 868 (47.7%) and 615 (33.8%), respectively. The patients with only haematuria (≥ 3 red blood cells/high-power field) were 238 (13.1%).

The number of patients who underwent a renal biopsy during each of the 5-year quartiles increased from 254 cases in 1987–91 to 629 cases during 2002–06 (Figure 1).

Glomerular diseases comprised 85.9% of the total biopsied cases. The most common primary GN was IgAN (28.3%), which was followed by MCD at 15.5% and MN at 12.3%. FSGS and MPGN accounted for only a small percentage of primary GN, and the most common

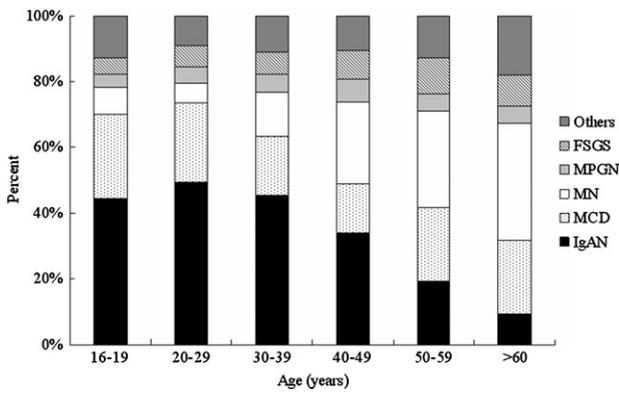


Fig. 2. Distribution of primary glomerular disease by age.

Table 2. Distribution of idiopathic nephrotic syndrome in Korea

	<i>N</i> = 611	(%)
Minimal change disease	235	38.5
Membranous nephropathy	157	25.7
IgA nephropathy	68	11.1
Focal segmental glomerulosclerosis	58	9.5
Membranoproliferative glomerulonephritis	51	8.3
Other	42	6.9

Table 3. Distribution in patients with HBsAg-positive in Korea

	<i>N</i> = 128	(%)
Membranous nephropathy	39	30.5
Membranoproliferative glomerulonephritis	27	21.1
IgA nephropathy	19	14.8
Minimal change disease	11	8.6
Focal segmental glomerulosclerosis	7	5.5
Other	25	19.5

secondary GN was systemic lupus erythematosus (8.7%) (Table 1).

Based on age, IgAN and MCD were mainly diagnosed between the 2nd and 4th decades of life. A diagnosis of normal or minor change was mainly made between the 2nd and 3rd decades, while MN was mainly diagnosed between the 6th and 8th decades (Figure 2).

MCD (38.5%), MN and IgAN were the most common primary GN of nephrotic syndrome in that order (Table 2). In patients who were younger than 40 years, MCD was the leading cause, while MN was the leading cause in patients who were older than 40 years (Figure 3). In total, 128 patients (7.4%) were HBsAg-positive, and MN (30.5%) and MPGN (21.1%) were the most common GN in these patients (Table 3).

The relative frequency of IgAN increased significantly from 25.6% in the first quartile (1987–91) to 34.5% in the last quartile (2002–06; $P < 0.01$). The relative frequency of MCD decreased significantly from 23.2% in the first quartile to only 7.0% in the last quartile ($P < 0.01$). The relative frequency of MPGN decreased significantly from

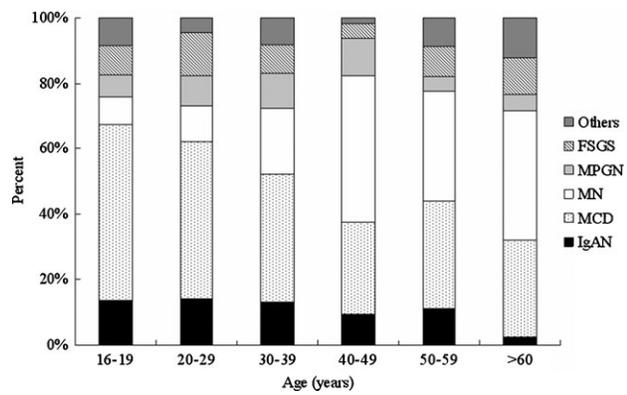


Fig. 3. Distribution of idiopathic nephrotic syndrome by age.

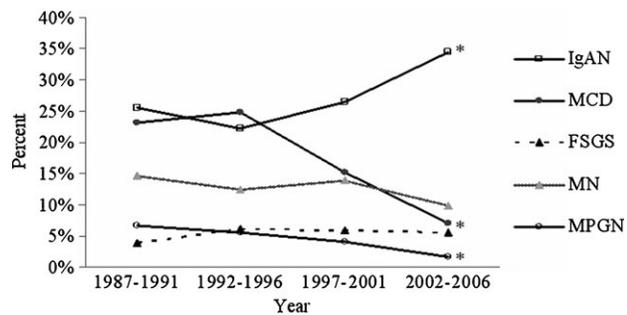


Fig. 4. Changing trends in biopsy-proven renal disease. * $P < 0.01$ compared with the three earlier time intervals.

6.7% in the first quartile to 1.7% in the last quartile ($P < 0.01$). The percentage of FSGS for each 5-year quartile did not show any trends, starting at 3.9% in the first quartile, increasing to 6.1% in the second quartile and decreasing slightly to 5.9% and 5.6%, respectively, for the last two quartiles (Figure 4).

Discussion

The number of renal biopsies increased during each time interval because of increased patient referrals for haematuria, proteinuria and presumed glomerular disease. The contributory cause of the increase in the number of renal biopsies was the larger Korean population in the last quartile (48 million in 2006) compared to the first quartile (42 million in 1987). The expanded pool of renal biopsies from patients with kidney disease in recent years makes the epidemiologic investigation more reliable. An improved technique for renal biopsy was also one of the causes.

We showed that IgAN is the leading cause of primary GN in adults, and the proportion of IgAN has significantly increased during the 20-year period of the study. In north-east Asian countries such as Japan and China, 45–50% of patients with primary GN had IgAN [7,8]. IgAN is the most common primary GN in Australia and some European countries such as Spain, Italy, France, The Netherlands and the Czech Republic [9–14]. Racial differences may account for geographic differences in the frequency of IgAN, because Asians may be more susceptible, whereas blacks may

be less susceptible [15]. The high prevalence may be related to genetic background, and evidence exists that IgAN is linked to a gene on chromosome 6q22–23 [16]. Variation in the detection also reflected regional differences in the recognition of asymptomatic microscopic haematuria or the frequency of renal biopsy. In countries where systematic screening for urinary abnormalities is performed, IgAN is the most frequent primary GN [17].

The reason for the increased frequency of IgAN is unknown. Changing referral patterns and attitudes towards biopsy for patients with asymptomatic urinary abnormalities are more likely explanations than more stable influences within a population, such as its genetic composition. The rise in the frequency is because of an increased number of patients with microscopic haematuria due to systematic screening for urinary abnormalities in Korea and may reflect changes in the frequency of detection rather than a true rise. Many patients with IgAN have only mild renal disease characterized by asymptomatic urinary abnormalities [18] and the role of a renal biopsy in the investigation of asymptomatic patients remains an issue. In Korea, Kim *et al.* [19] reported that 61.3% of patients with asymptomatic microscopic haematuria had IgAN. According to economic status, patients in wealthier countries with asymptomatic urinary abnormalities may be more likely to undergo biopsy, and therefore greater frequencies of IgAN may be diagnosed in these countries.

We showed the decline in the relative frequency of MCD. Korbet *et al.* [20] found that the incidence of MCD declined in their patient population from 25% for renal biopsies carried out from 1975 to 1984 to 11% for renal biopsies done from 1985 to 1994. In India, a reduction in the frequency of MCD has also been observed [21]. Therefore, MCD, commonly recorded in the Western literature as the important type of primary GN causing nephrotic syndrome in the past, has decreased remarkably. Children with nephrotic syndrome have not had a renal biopsy to provide the histologic proof of MCD, if they are corticosteroid responsive. However, adults with nephrotic syndrome should have a renal biopsy. The decreasing prevalence of MCD in our study is less likely due to unbiopsied nephrotic syndromes. Whether the change in the incidence is related to genetic background, environmental factors or frequent infections is uncertain.

We also observed a decline in the relative frequency of MPGN, which is common in adults, particularly in countries with a lower socioeconomic status. Hurtado *et al.* [6] proposed the hygiene hypothesis, according to which overcrowding and poor hygiene early in life may protect from atopic diseases because exposure to microbes favours a T helper cell 1-dominant response. An alteration in the immune balance of the T helper 1 and 2 subsets has been proposed to explain the predilection for MPGN to be associated with developing and poor nations.

We showed that the relative frequency of FSGS in Korea was 5.6%, with no difference according to the periods. Marked differences in the frequency and patterns of FSGS, however, exist worldwide. FSGS tends to be lower in northeast Asian countries (2–6%). In Europe, FSGS accounts for 6–15% of primary GN. In France, FSGS tended to decrease from 1976–80 to 1986–90 [22]. In contrast,

recent studies in the United States have shown that the frequency of FSGS is increasing and that it is the most common idiopathic glomerular disease [3,23]. Genetic variations may be important.

We showed that lupus nephritis is the most common cause of secondary GN in adults, although diabetic nephropathy is the most common renal disease occurring in many countries. This tendency might change in the next few decades as the incidence of diabetes mellitus is progressively increasing in Korea. Diabetic nephropathy is usually diagnosed without a renal biopsy in the absence of other clinical or serologic data suggesting another disease. Only a small minority of patients with diabetic nephropathy come to the renal biopsy.

In our study, the prevalence of non-glomerular renal diseases was 6.4%. The proportion of non-glomerular renal diseases was 6.5% in China [8]; however, the proportion of non-glomerular renal diseases in Italy [10] and the Czech Republic [11] was 14.7% and 14.8%, respectively. The reason for low prevalence is unknown. It may be related to genetic background, environment factors and indication of a renal biopsy.

A renal biopsy should be performed in the evaluation of adults presenting with idiopathic nephrotic syndrome. We showed that the most common primary GN of nephrotic syndrome is MCD (38.5%) followed by MN and IgAN. These data are similar to those of northeast Asian countries such as Japan [7] and some European countries such as Denmark [24]. In other European countries such as Spain and Italy, MN is the most common primary GN of nephrotic syndrome [10,18]. In the United States, MN was the most frequent cause of nephrotic syndrome before the early 1980s, but since 1995, FSGS has risen significantly to become the most common cause of adult nephrotic syndrome [25]. The reason for different aetiologies of nephrotic syndrome is unknown, but racial differences, nutritional behaviours and environmental factors may contribute to the difference.

We showed that the most common cause of GN in patients who were HBsAg-positive was MN, which was followed by MPGN and IgAN. The reported prevalence of hepatitis B virus (HBV)-associated nephropathy closely paralleled the geographic patterns in the prevalence of HBV [26]. A high HBsAg-positive rate was noted in Korea in an endemic area of hepatitis B. The overall seropositivity of HBsAg was 10.4% [27]. In Asian populations, MN is most frequently reported [28].

In conclusion, IgAN was the leading cause of primary GN, and MCD was the most common cause of nephrotic syndrome in Korea. In the 5-year quartile comparison, the relative frequency of IgAN increased, while the relative frequency of MCD and MPGN decreased significantly during the past 20 years. Because Korea does not maintain a nationwide GN registry, and it is not possible to use the database of public medical system, we do not show the incidence of GN. Therefore, we evaluate the prevalence of glomerular diseases at our institute, one of the largest hospitals in Korea. This study documents a change in the pattern of GN during the past 20 years, and this changing pattern of GN may reflect the changing pattern of socioeconomic and environmental factors in Korea.

Conflict of interest statement. None declared.

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Received for publication: 4.7.08; Accepted in revised form: 12.2.09