

Changing Incidence of Glomerular Disease in Olmsted County, Minnesota: A 30-Year Renal Biopsy Study

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Membranous nephropathy (MN) is considered the most common cause of nephrotic syndrome in white adults, but recent studies have shown an increasing incidence of focal segmental glomerulosclerosis (FSGS). These studies are difficult to interpret because the majority of cases came from urban tertiary referral centers. For validating these findings in the general population, trends in the incidence of various forms of glomerular disease (glomerulonephritis [GN]) among the residents of Olmsted County, MN were studied. Biopsy data of local patients who had a diagnosis of a nondiabetic glomerular disease from 1974 through 2003 were reviewed. Biopsies were categorized as (1) FSGS, (2) MN, (3) minimal change, (4) lupus nephritis, (5) membranoproliferative GN (MPGN), (6) IgA nephropathy (IgAN), (7) crescentic/necrotizing GN, and (8) other. Time trends in the annual age- and gender-adjusted (2000 US population) incidence rate per 100,000 Olmsted County population were estimated. A total of 195 biopsies were analyzed. Overall, IgAN was present in 22%, FSGS was present in 17%, and MN was present in 10%. Between 1974 to 1983 and 1994 to 2003, the incidence of any type of GN among Olmsted County residents increased more than two-fold ($P < 0.001$), FSGS by 13-fold ($P < 0.001$), and IgAN by three-fold ($P = 0.002$). Increases in MN were nonsignificant (2.5-fold; $P = 0.13$). Currently (1994 to 2003), the most frequent type of GN is IgAN (25%), followed by FSGS (20%) and MN (11%), with annual incidence rates of 2.1, 1.8, and 1.0 per 100,000/yr, respectively. This study confirms that the incidence of GN is growing overall, particularly for FSGS, which is the leading cause of nephrotic syndrome in white adults.

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In adults, membranous nephropathy (MN) traditionally has been considered the most common cause of nephrotic syndrome (NS). However, recent studies, mostly from Europe and Australia, have suggested a change in the pattern of glomerular diseases in the community: According to these, focal segmental glomerulosclerosis (FSGS) is increasing in incidence and now accounts for 20 to 25% of all adult NS cases (1–3). Furthermore, a recent study from the United States has shown FSGS to be the most common idiopathic glomerular disease in adults (4). However, that study included referral cases, and the increasing incidence of FSGS was seen only in the black (22.6%) and Hispanic (24.6%) populations and not in white individuals. Therefore, the findings of that study may not be generalized to the entire population of the United States, where 75% of the total is white. No current published studies have evaluated the trend and the pattern of glomerular disease in a well-defined white population in the United States. Therefore, to assess the validity of these findings in the general population, we studied the incidence of various forms of glo-

merular disease during the past 30 yr among the residents of Olmsted County, MN, who predominantly are white.

Materials and Methods

Olmsted County is uniquely suited for studies of this kind because medical care is virtually self-contained within the community and there are relatively few providers. Through the medical records linkage system provided by the Rochester Epidemiology Project, the details of almost all of the medical care delivered to the residents are available for study (5). Native kidney biopsy records were available for 375 Olmsted County residents, with 208 of these being GN, from the biopsy database at Mayo Clinic Rochester for the 30-yr period from 1974 through 2003. The data were assumed to be inclusive of all Olmsted County residents, because all renal biopsies from this community are performed and interpreted only at this center. However, 13 potential cases declined to authorize the use of their medical records for research in accordance with Minnesota privacy statutes (6). After approval by the Mayo Institutional Review Board, the remaining 195 patient charts were reviewed to obtain information about age, gender, and any possible secondary cause of glomerular disease. All biopsies had been evaluated with light microscopy, immunofluorescence, and electron microscopy, and a specific renal pathologist (D.J.L.) confirmed these diagnosis using standard diagnostic criteria. Patients with diabetic nephropathy were excluded from the study. Body mass index (BMI) and degree of proteinuria also were recorded in all patients with available data. Obesity was defined as a BMI >30 . Nephrotic-range proteinuria was defined as >3.5 g of proteinuria in 24 h. As anti-neutrophil cytoplasmic antibody testing was not routinely done before 1990, specific data regarding anti-neu-

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trophil cytoplasmic antibody positivity in patients with vasculitis were not collected.

Biopsies were categorized as (1) FSGS, (2) MN, (3) minimal change (MC), (4) lupus nephritis, (5) membranoproliferative glomerulonephritis (MPGN), (6) IgA nephropathy (IgAN), (7) crescentic/necrotizing GN, and (8) other/secondary GN. The overall crude biopsy rate per 100,000 population per year was calculated using the total number of renal biopsies done in each of the three time periods: 1974 to 1983, 1984 to 1993, and 1994 to 2003.

The relative frequencies of each type of GN were calculated for three 10-yr intervals. In calculating incidence rates, the entire population of Olmsted County was considered to be at risk. Denominator age- and gender-specific person-years were estimated from decennial census data (7). To obtain some sense of variability, we assumed that, given a fixed number of person-years, the number of GN cases follows a Poisson distribution. This allowed estimation of standard errors and the calculation of 95% confidence intervals (CI) for the incidence rates. Rates were directly age and gender adjusted to the population distribution of the United States in 2000. Even though the age and gender distribution of the Olmsted County is known, the distribution has changed over time. Because the current Olmsted County age distribution is similar to US age distributions, to facilitate comparisons, we used the more widely available 2000 US census age distribution. Comparison of the age- and gender-adjusted incidence of GN and specific GN subtypes among the three 10-yr periods was done using the *z* test. Summary quantitative data are reported as mean \pm SD or median (25th, 75th percentiles) as appropriate. All analyses were carried out in SAS (SAS Institute, Cary, NC), and *P* < 0.05 was considered significant.

Results

The biopsy registry identified 375 native renal biopsies in Olmsted County residents from 1974 to 2003. The crude annual renal biopsy rate (95% CI) increased significantly over time from 8.2 (6.4 to 10.0) to 8.8 (7.0 to 10.6) to 17.5 (15.1 to 19.9) per 100,000 for the periods 1974 to 1983, 1984 to 1993, and 1994 to 2003, respectively. The 2.1-fold increase from the period 1974 to 1983 to the period 1994 to 2003 was statistically significant (*P* < 0.001).

GN was diagnosed in a total of 208 of these biopsies in the past 30 yr. Thirteen patients refused access to their records for research, leaving 195 for analysis. GN was seen in 35 biopsies in 1974 to 1983 compared with 56 in 1984 to 1993 and 104 in 1994 to 2003, but the population grew in the interval from 92,006 (98% white) in 1980 to 106,470 (96% white) in 1990 to 124,277 (90% white) in 2000. The percentage of renal biopsies with GN was 52% overall, with the rate relatively stable during the three time periods (47, 62, and 49%; *P* = 0.08). Overall, the most frequent primary GN diagnoses were IgAN (*n* = 42), FSGS (*n* = 33), lupus (*n* = 25), and MN (*n* = 20), followed by MPGN (*n* = 13), necrotizing (*n* = 12) and crescentic (*n* = 10) GN, and MC (*n* = 8). GN was secondary to other conditions in 32 patients.

The mean \pm SD age at the time of GN biopsy was 44 \pm 20 yr, and 111 (56.9%) were male. Median (25th, 75th percentiles) serum creatinine values at time of GN biopsy increased slightly over time (*P* = 0.10), being 1.2 (0.9, 2.2), 1.4 (0.9, 2.1), and 1.5 (1.1, 2.6) for years 1974 to 1983, 1984 to 1993, and 1994 to 2003, respectively. Median 24-h urine protein was somewhat higher (*P* = 0.052) in later years, being 1.7 (1.2, 3.4), 3.7 (1.9, 7.0), and

2.8 g (1.2, 7.3) for the periods 1974 to 1983, 1984 to 1993, and 1994 to 2003, respectively.

The overall annual incidence of GN in this population was 6.6 per 100,000, directly age and gender adjusted to the population structure of the United States in 2000. As noted in Table 1, the GN incidence rate was 7.9 per 100,000 person-years in male individuals compared with 5.4 per 100,000 person-years in female individuals (*P* = 0.006). There was a 2.3-fold increase in the incidence of any GN from the period 1974 to 1983 to the period 1994 to 2003 (*P* < 0.001), as the annual incidence of GN increased from 3.9 per 100,000 (95% CI 2.6 to 5.3) in 1974 to 1983 to 9.0 per 100,000 (95% CI 7.3 to 10.7) in 1994 to 2003 (Table 1). The age-specific incidence generally increased for both genders, peaking at 60 to 79 yr then decreasing after age 80.

The incidence of specific glomerular diseases in Olmsted County is summarized in Table 2 and Figure 1 by time period. For the most recent time period, 1994 to 2003, the annual incidence for any GN was 9.0 per 100,000 (95% CI 7.3 to 10.7), for FSGS was 1.8 per 100,000 (95% CI 1.0 to 2.6), and for IgAN was 2.1 per 100,000 (95% CI 1.3 to 3.0). Compared with the 2.3-fold increase in the incidence of any GN from the period 1974 to 1983 to the period 1994 to 2003, the incidence of FSGS increased 13-fold (from 0.14 to 1.8 per 100,000) during the same time period (*P* < 0.001), whereas the incidence of IgAN showed a three-fold increase (*P* = 0.002). However, the incidence of MN did not increase significantly from the period 1974 to 1983 to the period 1994 to 2003 (2.5-fold; *P* = 0.13). There was a significant change (5.6-fold; *P* = 0.001) in the overall incidence of other glomerular diseases (other/secondary includes postinfection [*n* = 7], amyloidosis [*n* = 5], end stage [*n* = 6], cancer-related immune complex GN [*n* = 1] and MN [*n* = 1], HIV nephropathy [*n* = 1], cryoglobulinemia [*n* = 1], and insufficient tissue for diagnosis [*n* = 10]). As expected on the basis of the relative trends in incidence rates, the percentage of biopsies with FSGS increased with time, being 5, 17, and 20% for years 1974 to 1983, 1984 to 1993, and 1994 to 2003, respectively, as did the percentage that were IgAN (18, 15, and 25%). The percent of biopsies with secondary diagnoses was stable over time (29, 29, and 28%) as was the percentage with MN (9, 11, and 11%), whereas decreases were seen for necrotizing or crescentic (17, 11, and 10%) and MC (9, 5, 2%).

Among all patients who had FSGS and for whom data on race were available (*n* = 28), there were 23 white and two black patients. The mean BMI of patients with FSGS (*n* = 26) was 28 \pm 8.41, and there were no more patients who had FSGS and BMI >30 in 1994 to 2003 (six of 17) than in 1974 to 1983 (zero of one) or 1984 to 1993 (two of eight). In 1984 to 1993, 67% (four of six) patients with FSGS presented with nephrotic-range proteinuria compared with 78% (14 of 18) in 1994 to 2003. The mean 24-h proteinuria in patients with FSGS was 6.1 \pm 4.9 g. Secondary causes of FSGS could be identified in no patient in 1974 to 1983, in two patients in 1984 to 1993 (reflux nephropathy [*n* = 1] and Alport's syndrome [*n* = 1]), and one patient in 1994 to 2003 (HIV related).

Table 1. Incidence of any glomerular disease among Olmsted County, Minnesota, residents by gender, age, and time period

	1974 to 1983		1984 to 1993		1994 to 2003		All Years	
	<i>n</i>	Rate ^a	<i>n</i>	Rate ^a	<i>n</i>	Rate	<i>n</i>	Rate ^a
Male (yr)								
0 to 9	0	0.0	2	2.3	1	1.1	4	1.2
10 to 19	3	3.7	4	5.4	5	5.5	12	4.9
20 to 29	3	4.0	6	7.5	6	7.5	15	6.4
30 to 39	2	3.0	8	8.9	10	10.0	20	7.8
40 to 49	3	6.3	4	6.3	12	13.1	19	9.4
50 to 59	2	5.5	5	11.2	10	16.7	17	12.1
60 to 69	4	16.3	5	16.7	6	15.9	15	16.3
70 to 79	0	0.0	5	28.6	4	16.8	9	16.3
≥80	0	0.0	0	0.0	1	8.6	1	3.9
subtotal	17	4.3 ^b	39	8.5 ^b	55	9.7 ^b	111	7.9 ^b
Female (yr)								
0 to 9	1	1.3	1	1.2	0	0.0	2	0.8
10 to 19	6	7.5	4	5.5	0	0.0	10	4.2
20 to 29	4	4.3	2	2.2	7	8.3	13	4.9
30 to 39	2	2.9	2	2.1	6	5.9	10	3.8
40 to 49	1	2.1	3	4.5	6	6.2	10	4.8
50 to 59	1	2.6	2	4.5	8	12.6	11	7.5
60 to 69	3	9.9	1	2.9	11	26.8	15	14.2
70 to 79	0	0.0	2	7.4	7	22.0	9	10.9
≥80	0	0.0	0	0.0	4	15.0	4	6.4
subtotal	18	3.6 ^b	17	3.4 ^b	49	8.1 ^b	84	5.4 ^b
Total	35	3.9 ^c	56	5.8 ^c	104	9.0 ^c	195	6.6 ^c

^aIncidence per 100,000 person-years.

^bIncidence per 100,000 person-years directly age-adjusted to structure of total US population in 2000.

^cIncidence per 100,000 person-years directly age- and gender-adjusted to structure of total US population in 2000.

Discussion

MN was thought by far to be the most common cause of NS in adults, especially in the white population. Recent studies, however, have shown an increase in the incidence of FSGS (2,4,8), and a similar trend was found in our study. Our study is unique insofar as it was conducted among unselected patients from the community of Olmsted County. The majority of the population resided in Rochester (85,806 of 124,277 in 2000), the urban center of an otherwise rural area that has an overwhelmingly white population (90% in 2000) of predominantly Northern European extractions, and we report the increasing incidence of FSGS in this population also.

D'Agati and colleagues (9,10) noted a seven-fold increase in the incidence of FSGS in their renal biopsy database from 1974 to 1993. Subsequently, Haas *et al.* (3) confirmed the increasing incidence of FSGS among adult nephropathies, observing a three-fold increase from 1974 to 1993. More recently, Kitiyakara *et al.* (11) showed that ESRD as a result of FSGS has increased 11-fold in the past 2 decades and observed that the incidence rate for FSGS related ESRD was four-fold greater in black than white patients. Even though these studies showed an increasing incidence of FSGS in white as well as black adults, clearly the findings were more impressive for the black population,

and collapsing GN (seen most often in black patients) constituted up to 4.7% of all patients with FSGS. Furthermore, they included referral cases from metropolitan areas with different racial backgrounds (3,4,8). This may restrict extension of these observations to the general population of the United States, which is predominantly white. However, the findings in our study confirm these observations in the white population and suggest that factors other than race are responsible for the increasing incidence of FSGS. Significantly, collapsing FSGS was not observed in any patient in our study and does not explain the increasing incidence. Urbanization, a suggested explanation for the increase in the incidence of other GN, such as MC, and the progressive increase in the frequency of obesity may play a role in the increasing incidence of FSGS. However, as noted from the findings of our study, in which there was no increase in incidence of obesity in patients with FSGS during the three periods, obesity is unlikely to be the major factor to account for increasing incidence of FSGS (12,13), and involvement of yet-unidentified new environmental factors in the causation of FSGS remains an intriguing possibility.

Korbet *et al.* (14) noted a decrease in the incidence of MN in black individuals compared with an increase of approximately 10% over 10 yr in the white individuals. Later, Braden *et al.* (4)

Table 2. Incidence of specific glomerular diseases among Olmsted County, Minnesota, residents in 1974 to 2003, by time period^a

GN Subtype	1974 to 1983		1984 to 1993		1994 to 2003		All Years	
	<i>n</i>	Rate ^b (95% CI)	<i>n</i>	Rate ^b (95% CI)	<i>n</i>	Rate ^b (95% CI)	<i>n</i>	Rate ^b (95% CI)
IgAN	7	0.7 (0.2 to 1.2)	9	0.9 (0.3 to 1.5)	26	2.1 (1.3 to 3.0)	42	1.4 (1.0 to 1.8)
FSGS	1	0.1 (0.0 to 0.4)	11	1.1 (0.4 to 1.7)	21	1.8 (1.0 to 2.6)	33	1.1 (0.7 to 1.5)
MN	3	0.4 (0.0 to 0.8)	6	0.7 (0.1 to 1.3)	11	1.0 (0.4 to 1.5)	20	0.7 (0.4 to 1.0)
MC	3	0.4 (0.0 to 0.8)	3	0.3 (0.0 to 0.6)	2	0.2 (0.0 to 0.4)	8	0.3 (0.1 to 0.5)
MPGN	1	0.1 (0.0 to 0.3)	6	0.6 (0.1 to 1.0)	6	0.5 (0.1 to 0.9)	13	0.4 (0.2 to 0.7)
Lupus nephritis	10	1.0 (0.4 to 1.6)	7	0.7 (0.2 to 1.2)	8	0.7 (0.2 to 1.1)	25	0.8 (0.5 to 1.1)
Necrotizing GN	2	0.3 (0.0 to 0.7)	2	0.3 (0.0 to 0.6)	8	0.7 (0.2 to 1.2)	12	0.4 (0.2 to 0.7)
Crescentic GN	5	0.7 (0.1 to 1.3)	3	0.4 (0.0 to 0.9)	2	0.2 (0.0 to 0.4)	10	0.4 (0.1 to 0.6)
Other secondary ^c	3	0.3 (0.0 to 0.7)	9	0.9 (0.3 to 1.6)	20	1.8 (1.0 to 2.6)	32	1.1 (0.7 to 1.5)
All GN	35	3.9 (2.6 to 5.3)	56	5.8 (4.3 to 7.4)	104	9.0 (7.3 to 10.7)	195	6.6 (5.7 to 7.6)

^aCI, confidence interval; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; IgAN, IgA nephropathy; MC, minimal change; MN, membranous nephropathy; MPGN, membranoproliferative GN.

^bIncidence/100,000 person-years directly age-adjusted to structure of total US population in 2000.

^cOther secondary includes postinfection (*n* = 7), amyloidosis (*n* = 5), end-stage (*n* = 6) and cancer-related immune complex GN (*n* = 1) and MN (*n* = 1), HIV nephropathy (*n* = 1), cryoglobulinemia (*n* = 1), and insufficient tissue for diagnosis (*n* = 10).

also observed a similar decrease in the incidence of MN in the US population, but they noted a decrease in incidence in both white and black individuals. The findings in our study, in which the incidence of MN did not change significantly during the past 30 yr, contrasts with these observations in the past and confirms the findings from a study by Haas *et al.* (3). Note, however, that we could not assess trends in nonwhite individuals, who represented only 2% of the population in 1980 and

10% in 2000 (0.4 *versus* 2% black) and who, moreover, were much younger on average than the majority population.

Although rare in black individuals, IgAN remains the most common biopsy-proven GN in adults, and especially in Hispanic individuals (14). The results of our study extend this finding to the white population also. It is interesting to note that the incidence of IgAN increased three-fold from the first 10-yr period to the last 10-yr period, and part of this increase could be attributed to a two-fold increase in renal biopsy rate in the same time frame. Haas *et al.* (3,8) observed a similar increasing trend for IgAN, but the cause for this increase in incidence also remains unexplained. It is interesting to note that the overall incidence of GN was higher in male than in female individuals, and the incidence of GN progressively increased for both genders during the three periods.

Although the results of our study need to be interpreted in the context of an increasingly aggressive diagnostic approach to glomerular diseases, this is unlikely to be the main reason for the increasing incidence of FSGS because of the following reasons. First, the degree of elevation in serum creatinine and the severity of proteinuria at the time of renal biopsy were not less in the later time periods. Second, the percentage of all biopsies that were GN remained fairly stable during the three time periods between 1974 to 2003, and the incidence of other GN-like MN did not show a similar trend in the same population. Third, the overall annual incidence of GN in Olmsted County in the most recent time period was in fact slightly less than that reported from Victoria, Australia (9.0 per 100,000 here *versus* 12.4 per 100,000 in Australia, both age and gender adjusted to the US 2000 population), and the renal biopsy rate in this community (12 per 100,000 per year in 1974 to 2003) was significantly lower than that reported by Briganti *et al.* (2) (21.5 per 100,000; 1147 per 2030 with 57% with GN). Also, the inci-

Annual Olmsted County Age- Sex-Adjusted Rate per 100,000

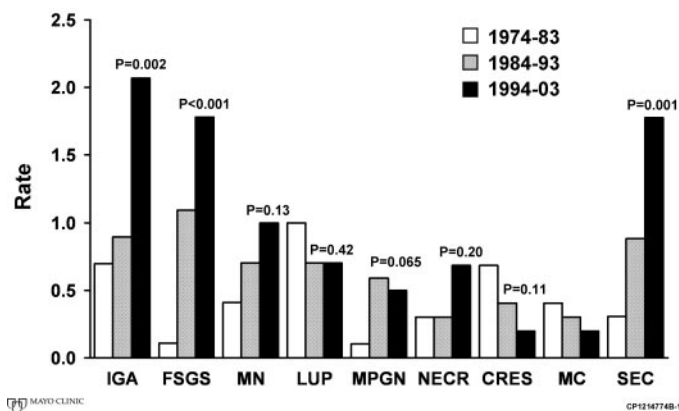


Figure 1. Annual age- and gender-adjusted incidence rates of specific glomerular diseases among Olmsted County, MN, residents in 1974 to 2003, by time periods. IgA, IgA nephropathy; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy; LUP, lupus nephritis; MPGN, membranoproliferative GN; NECR, necrotizing GN; CRES, crescentic GN; MC, minimal change; SEC, other secondary GN.

dence of FSGS increased 13-fold between 1973 to 1983 and 1994 to 2003 compared with a corresponding increase of only 2.1-fold in population-adjusted annual crude renal biopsy rates. Last, the annual incidence of GN subtypes (age and gender adjusted to the US 2000 population) in Olmsted County (1994 to 2003) and Australia (1995 to 1997) are comparable (FSGS 2.1 versus 1.8; MN 1.3 versus 1.0; and IgAN 4.2 versus 2.1 per 100,000, respectively).

There are some limitations of our study. Because this is a renal biopsy-based study and not all patients with GN undergo renal biopsy, our results potentially could underestimate the true number of patients with primary glomerular disease in the population. Also, we cannot exclude the possibility that a few patients from this county were seen and biopsied at centers elsewhere. Despite these limitations, the findings in our study are unique and best represent the US white population. Our study confirms that the incidence of GN is growing overall, particularly so for FSGS, which in our data are second only to IgAN as the leading cause of GN in white adults and is the most common cause of NS.

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