Evaluation and Outcome of Proteinuria in Older and Younger Adults

Kalathil K. Sureshkumar, 1 Tarang Ray, 2 and Barbara A. Clark 1

1Division of Nephrology and Hypertension and
2Department of Internal Medicine, Allegheny General Hospital, West Penn Allegheny Health System, Pittsburgh, Pennsylvania.

Background. The spectrum of proteinuric renal disease in older adults remains incompletely defined. The purpose of the present study was to determine if differences exist in diagnostic approach, etiology, therapy, and outcome between older (≥60 years) and younger (<60 years) patients referred for evaluation of proteinuria.

Methods. We conducted a retrospective review of outpatient office charts in a 7-physician, hospital-based nephrology practice.

Results. We identified 69 patients with at least 1 subsequent follow-up assessment after reviewing approximately 500 sequential charts. Forty-five were younger (mean ± SD age, 38 ± 2 years), and 24 were older (69 ± 1 years). The degree of proteinuria at presentation was similar (4.5 ± 0.7 vs 3.9 ± 0.6 g/dl, older vs younger, p = NS), but older patients had higher creatinine levels (1.7 ± 0.2 vs 1.2 ± 0.07 mg/dl, p < .01), lower creatinine clearances (64 ± 7 vs 111 ± 7 ml/min, p < .05), and higher systolic blood pressure (164 ± 8/88 ± 2 vs 145 ± 4/94 ± 2 mm Hg, p < .01). Older patients were more likely to decline a renal biopsy (21% vs 7.6%, p < .01). The most common final renal diagnoses were immunoglobulin A nephropathy (31%), focal segmental glomerulosclerosis (24%), hypertension (13%), and membranous nephropathy (11%) in the younger patients, and membranous nephropathy (29%), hypertension (25%), diabetic nephropathy (17%), and minimal change disease (8%) in the older patients. Steroids were given to 17.7% of younger patients and 16.7% of older patients (p = NS). The percentage of patients with improvement, defined as a 50% reduction in proteinuria with stable or improved renal function, was similar among older and younger patients (33.3% vs 35.5%). However, older patients were more likely to develop progression of renal disease (33.3% vs 8.8%) and less likely to retain stable renal function (29.2% vs 53.3%).

Conclusion. Significant differences exist in proteinuric renal disease between older and younger adults.

The true spectrum of glomerular disease in the elderly is difficult to establish. Although there have been several published renal biopsy series, these do not fully reflect the underlying disease spectrum as not all patients presenting for evaluation of proteinuria undergo renal biopsy. Patients with an established disease, such as diabetes or hypertension, or with lower levels of proteinuria may not be referred for biopsy. The most common causes for referral for biopsy outlined in other studies are nephrotic syndrome and renal function impairment (1). There may also be reluctance on the part of the patient to undergo invasive testing. No prior studies have addressed whether the diagnostic approach to the proteinuric patient, with respect to number and types of testing and referral for renal biopsy, differ based on the age of the patient. It is also not known if recommendations for therapeutic trials, such as steroids or angiotensin-converting enzyme inhibition differ based on age and whether elderly patients have a different rate of decline in renal function on follow-up. The purpose of the present study was to determine if differences exist in diagnostic approach, etiology, therapy, and outcome between older patients and younger patients referred for evaluation of proteinuria.

Methods
We conducted a retrospective review of outpatient office charts in a 7-physician, hospital-based nephrology practice. Patients were chosen for inclusion in the study if the primary reason for referral was proteinuria and if data from at least 1 follow-up visit were available. Patients with all degrees of proteinuria were included in the study, and nephrotic-range proteinuria was defined as greater than 3 g of protein per 24-hour urine collection. Patients were included in the younger age group if age at presentation was less than 60 years and in the older age group if age at presentation was 60 years or older. Improvement was defined as at least a 50% reduction in the degree of proteinuria with stable or improved renal function. Progression of renal disease was defined as a rise in serum creatinine of at least 0.3 mg/dl on last follow-up. Comparison between groups was made using Chi-square analysis and comparison of proportions. Results were considered statistically significant at a p value of <.05.

Results
We identified 69 cases after reviewing approximately 500 active charts. Forty-five were younger (mean ± SD age, 38 ± 2 years), and 24 were older (69 ± 1 years). In the younger age group, 36 patients were white, 7 were black, and 2 were other races; in the older age group, 23 patients were white, and 1 patient was black. Characteristics at the time of presentation, mean duration of follow-up, and characteristics at last follow-up in each group are depicted in Table 1. The degree of proteinuria at presentation was similar, but older patients had higher serum creatinine levels, lower creatinine clearance, and higher systolic blood pressure.
pressure. Comorbidities were more prevalent in the older patients, but the difference between groups was not statistically significant.

Table 2 depicts the frequency of diagnostic testing ordered in each group and the percentage of patients with abnormal results. There were no significant differences in the number of noninvasive tests ordered. However, the specific type of testing differed somewhat in that serum protein electrophoresis was more frequently ordered in older than in younger patients, and determination of immunoglobulin A (IgA) levels was more frequently ordered in younger compared with older patients. Renal biopsy was recommended with equal frequency in younger and older patients. Patients in the older age group were more likely to decline a biopsy (21% vs 7.6%, p < .05) (Table 1).

Figure 1 depicts the diagnoses in each group. These are listed as *presumptive* diagnoses if they were made on clinical criteria alone or as *biopsy-proven* diagnoses in cases in which biopsy was performed. Presumptive diagnosis of IgA nephropathy was usually made on the basis of microhematuria and proteinuria outside of the nephrotic range. A presumptive diagnosis of focal segmental glomerulosclerosis (FSGS) was made if patients had more marked proteinuria, bland urine sediment, obesity, or a solitary functioning kidney. The biopsy diagnosis matched the initial presumptive diagnosis in 46% of younger patients and 60% of older patients. In the younger patients, the most common final diagnoses were IgA nephropathy (31%), FSGS (24%), hypertension (13%), and membranous nephropathy (11%). In the older patients, the most common final diagnoses were membranous nephropathy (29%), hypertension (25%), diabetic nephropathy (17%), and minimal change disease (MCD) (8%). Microhematuria was present in 71% of patients with IgA nephropathy, 43% of patients with FSGS, 45% of patients with membranous nephropathy, and 8% of patients with hypertension. Patients with IgA nephropathy and hypertension as the underlying diagnosis had a lesser degree of proteinuria (2.2 ± 0.5 g/d and 1.5 ± 0.5 g/d, respectively) than patients with FSGS (5.6 ± 1.6 g/d), membranous nephropathy (5.7 ± 1.8 g/d), diabetes mellitus (5.2 ± 1.0 g/d), and MCD (18 ± 2.0 g/d).

The therapeutic recommendations did not differ between younger and older patients. Corticosteroid therapy was given to 17.7% of younger patients and 16.7% of older patients (p = NS). Angiotensin-converting enzyme (ACE) inhibitor therapy was given to 71% of younger patients and 70.8% of older patients (p = NS). One patient in each group was treated with cytotoxic therapy (cyclophosphamide for membranous nephropathy in 1 younger patient and chemotherapy for light chain deposition disease in 1 older patient). Treatment changed after biopsy in 29% of younger patients and 12.5% of older patients. Thirty patients had nephrotic-range proteinuria. Of these, 17 were younger and...
13 were older. Of patients with nephrotic-range proteinuria, 41% of younger patients and 31% of older patients were treated with steroids (p = NS).

Outcomes are depicted in Table 1. Length of follow-up was similar in younger and older patients. In both groups, blood pressure decreased, serum creatinine levels increased, and the extent of proteinuria decreased. An improvement in proteinuria (defined as at least a 50% reduction in the degree of proteinuria) was seen in 16 of 45 younger patients (35.5%) and 8 of 24 older patients (33.3%) (p = NS). Of these patients with improvement, 4 in each group received prednisone therapy. Progression of renal disease (rising serum creatinine level) occurred in 4 of 45 younger patients (8.8%), with 2 developing end-stage renal disease. Progression of renal disease occurred in 8 of 24 older patients (33.3%) (p < .05 older vs younger), with 1 developing end-stage renal disease. At last follow-up, 24 of 45 younger patients (53.3%) and 7 of 24 older patients (29.2%) had no change in the degree of proteinuria or renal function.

**DISCUSSION**

Proteinuria is one of the most frequent modes of presentation of underlying renal disease. The frequency of the presence of proteinuria in randomly collected urine specimens increases with aging and is significantly associated with increasing mortality (2). Since the life expectancy of humans continues to increase, a better understanding of proteinuric renal disease in the elderly is relevant.

Our study confirms membranous nephropathy as the leading diagnosis in older patients presenting with proteinuria, consistent with an earlier study (3). In contrast, a recent renal biopsy study suggested that the etiology of proteinuric renal disease has been changing in adults, with FSGS emerging as the leading cause (4). This difference could be related to the relatively younger age of the patients in the aforementioned study. Another factor could be the small number of black patients in our study. Our study also supports treating older patients as aggressively as younger patients, as remission rates were similar in these 2 groups. However, older patients present with more advanced degrees of renal insufficiency, which may be a factor in the more significant deterioration of their renal function over time compared with that of younger patients.

In the younger population, the most common diagnoses were IgA nephropathy and FSGS. If nephrotic-range proteinuria (>3 g/24 h) had been an inclusion criterion, FSGS would have been the leading diagnosis in the younger patients, followed by IgA nephropathy. The spectrum of diagnoses in the younger patients is similar to that reported in other recent studies of proteinuric renal disease, with an increased prevalence of FSGS (particularly in the black population) and IgA nephropathy (5). The individuals in our study were predominantly white, and it was therefore not possible to determine racial differences in the prevalence of disease. Prior studies examining biopsy diagnoses in the past decade (1990s) compared with the 1970s have reported a decline in the incidence of membranous glomerulonephritis and MCD and an increase in the incidence of FSGS and IgA nephropathy as a cause of nephrotic syndrome in adults. Our study supports these observations in the young adult population (age <60 years) but not in an older adult population, in which membranous nephropathy still appears to be the leading diagnosis. Because we wished to look at the incidence of all potential causes of proteinuric renal disease across the spectrum of age, including secondary disease, proteinuria was also frequently attributed to hypertension and diabetes, particularly in the older population.

Initial diagnostic workup and treatment plans did not significantly differ between the 2 groups, even though the older patients were more likely to decline a renal biopsy. A renal biopsy was recommended in 55% to 60% of patients.
This percentage may have been higher had only patients with nephrotic-range proteinuria been included or had patients with presumed diabetic nephropathy or hypertensive nephrosclerosis been excluded. Although a significant number of patients had diagnoses made on clinical grounds alone, it should be noted that presumptive clinical diagnoses did not always match biopsy diagnoses in those who underwent renal biopsy. This observation would potentially support a more aggressive approach favoring biopsy in certain patients. Perhaps biopsies should be more aggressively pursued in both younger and older patients to better clarify diagnoses, although the impact of this approach on therapy is not clear. The reasons for declining biopsy were not routinely given. There appears to be an increased reluctance of elderly patients to undergo invasive diagnostic testing. Noninvasive diagnostic testing was occasionally useful, particularly for detecting IgA nephropathy: IgA levels were increased in 43% of those with IgA nephropathy in whom IgA levels were checked. Testing of antinuclear antibody levels was less useful in the older patients, in whom false-positive results occurred in 17%.

We noted an important difference in the serum creatinine levels and the creatinine clearance between patients younger than 60 years and patients aged 60 years and older at the time of presentation (1.2 ± 0.07 vs 1.7 ± 0.27 mg/dl and 111±7 vs 64 ± 7 ml/min., respectively) and at last follow-up (1.6 ± 0.3 vs 2.5 ± 0.6 mg/dl and 99 ± 6 vs 58 ± 8 ml/min., respectively). Part of this finding could be related to the known decline in renal function with aging and the loss of functional renal reserve. The decline in creatinine clearance begins in the mid-30s at a rate of 8 ml/1.73 m² per minute per decade. The cumulative effects of an aging vascular system, with an increased prevalence of atherosclerosis, hypertension, and diabetes mellitus, have been cited as contributing factors (6). In our study, patients older than 60 years had increases in both systolic blood pressure and prevalence of diabetes. These comorbidities likely contributed to more advanced renal disease at presentation for evaluation of proteinuria and may also have contributed to a subsequent more rapid decline in renal function at follow-up as compared with younger patients.

Even in normal aging, there is a 30% to 50% decrease in the number of functioning glomeruli with an increasing number of sclerotic glomeruli with aging. The remaining glomeruli show a decrease in surface area, an expansion of the mesangial area, and an increase in basement membrane thickness. A variety of factors may play a role in these changes, including hemodynamic effects, overexpression of growth factors, excessive accumulation of reactive oxygen intermediates, cytokines, and advanced glycosylation end products (6). All of these changes lead to a decline in the renal functional reserve with aging. Therefore, the ability of the aging kidney to contain any injury may be diminished with factors contributing to more aggressive injury when there is underlying injury to begin with. The higher incidence of progressive renal disease in the older patients despite similar frequency of use of ACE inhibitors might support this theory.

The increased prevalence of proteinuric renal disease and nephrotic syndrome in the elderly has been attributed to a variety of factors. Changes in immune status that occur with the aging process have been implicated. For instance, abnormalities in T-cell function have been said to be important in the development of MCD. Although MCD is primarily a disease of children, the incidence increases again with advancing age. Certain types of malignancies are associated with the nephrotic syndrome (7), and the incidence of malignancies increases with age. Other contributing factors may include the final common pathway of hyperfiltration leading to glomerulosclerosis (8) and age-related changes in the biochemical composition of the glomerular basement membrane, with a decrease in the quantity of collagenous components (9).

It is reassuring to note that a similar percentage of patients in each group (35.5% vs 33.3%) had a response to therapy with improvement in renal function (defined as a 50% reduction in the degree of proteinuria with stable or improved renal function). This finding justifies an aggressive approach in treating nephrotic syndrome in elderly patients.

In summary, diagnostic and therapeutic recommendations for proteinuric renal disease are similar regardless of age at presentation. IgA nephropathy and FSGS were the most common diagnoses in the younger patients studied, compared with membranous nephropathy in the older patients. Older patients had comparatively higher serum creatinine levels, lower creatinine clearance, and higher systolic blood pressure at presentation. Older patients were more likely to decline a renal biopsy. Rates of remission/improvement were similar in older and younger patients. However, among patients not achieving remission, older patients were more likely to develop progressive renal failure.

ACKNOWLEDGMENTS

Address correspondence to Barbara A. Clark, MD, Division of Nephrology and Hypertension, Allegheny General Hospital, 4th Floor South Tower, 320 E. North Ave., Pittsburgh, PA 15212. E-mail: rshannon@wpahs.org.

REFERENCES