

# Chapter 10: Glomerular Disease in the Elderly

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## APPROACH TO AND UNIQUE FEATURES OF GLOMERULONEPHRITIS IN ELDERLY PERSONS

Recognition, diagnosis, and management of glomerular disease in elderly persons have several unique challenges. Reductions in GFR are common in individuals over the age of 75. Because this so often occurs in the setting of aging nephropathy, hypertension, or vascular disease, other intrinsic kidney diseases are not considered in the differential diagnosis. Aging nephropathy is characterized by loss of GFR of approximately 1.7 ml/min per year<sup>1</sup>; thus, renal function seems to be stable over a several year window of time. However, this can represent a significant loss of renal function over the final 30 yr of life. Within a short time frame, any change in renal function should indicate the possibility of an alternative diagnosis. When prior measures of renal function are not available, estimation of GFR using the Cockcroft-Gault formula or another formula that takes into account age and an assumed serum creatinine of 0.8 mg/dl will allow calculation of a rough estimate of age-adjusted GFR. Should the measured eGFR be substantially below that predicted on the basis of age alone, other diagnoses should be considered. Using analysis of large databases, O'Hare *et al.*<sup>2,3</sup> have shown that aging nephropathy *per se* is not usually associated with proteinuria. Because many of these individuals have not been subjected to renal biopsy, the actual pathology is unknown; however, some have argued that the absence of proteinuria excludes significant pathology. Based on these arguments, the presence of proteinuria or active urinary sediment should be considered as evidence of renal disease other than age-associated reduction in GFR,<sup>4,5</sup> and the possibility of glomerulonephritis (GN) should be considered. Despite these caveats, urinary abnormalities and reductions in GFR are frequently erroneously attributed to aging *per se* and not pursued further, thus depriving the elderly individual

of the benefit of diagnosis and appropriate intervention.

## GENDER-, ETHNIC-, AND AGE-RELATED DISPARITIES IN HEALTHCARE

Studies continue to show that underrepresented minorities, women, and elderly persons are provided standard care and included in clinical trials at rates below those for white men<sup>6,7</sup>; however, these same groups have higher rates of certain diseases and worse outcomes. This relatively poorer prognosis argues for a more aggressive approach. Given that women make up a steadily higher proportion of the elderly population with each year of increasing age, disparities in approach to their care is even more relevant in this age group. With any given disease, women lose renal function at a slower rate than men until after menopause when this benefit is lost. Recognition of changes in risk factors and incidence of specific forms of GN throughout the lifespan is critical to resolving health disparities.

## URINARY PROTEIN EXCRETION IN ELDERLY PERSONS

Standard teaching often taught that urinary protein excretion increases with age. Because these concepts were developed based on studies of subjects living in nursing homes, it was thought that these data reflected disease, often urinary tract infection, and thus were thought not to be relevant to the elderly population at large. Subsequent studies<sup>8</sup>

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showed that healthy elderly subjects generally do not have proteinuria; however, in those who do, there is significant loss of renal function over 5 yr of follow-up. Recent studies have shown that rates of albuminuria in community-dwelling elderly subjects increase with age and may reach 37% in individuals over the age of 80.<sup>9</sup> As in other age groups, the presence of albuminuria shows increased risk for dementia,<sup>9</sup> hypertension, cardiovascular disease, and progressive renal disease. Based on these findings, proteinuria in elderly individuals should be viewed as an indicator of renal disease and a predictor of other disorders that have implications for diagnosis, therapy, and outcomes. These findings are somewhat difficult to reconcile with epidemiologic database studies such as those reported by O'Hare *et al.*, which indicate that elderly individuals with GFR <60 ml/min usually do not have proteinuria. Additional studies are needed to clarify the nature and natural history of aging nephropathy *per se*; but all studies indicate that, when proteinuria is present, specific diagnoses are usually identified on biopsy and outcomes are poorer.

## RENAL BIOPSY IN ELDERLY PERSONS

Despite the frequency of urinary abnormalities and reductions in GFR among elderly individuals, only 15% of renal biopsies are from individuals over the age of 65 and even fewer are in individuals over the age of 75. As a result, very few data are available that inform our understanding of GN in elderly individuals.<sup>5</sup> The limited number of biopsies in the face of high rates of proteinuria suggests that many older individuals with kidney disease are not provided a specific diagnosis or offered disease-specific treatments to slow the rate of progression. It is well documented that inflammatory symptomatology and thus clinical manifestations are blunted in elderly persons, which leads to atypical presentations even for common diseases. This also can contribute to missed or delayed diagnosis in this age group. Nephrotic syndrome is often misdiagnosed as congestive heart failure. As elderly individuals with nephrotic syndrome had focal sclerosis (FSGS; 23%), minimal change disease (MCD; 19%), and membranous nephropathy (MN; 15%), therapeutic intervention would be expected to modify their outcomes. Among those individuals with an acute nephritic syndrome, most had pauci-immune, MPO-ANCA positive, crescentic GN, whereas the remainder had acute interstitial nephritis.<sup>10</sup> One study focused on individuals over the age of 80 (3% of the biopsies in their series).<sup>11</sup> Similar to the previous study, with advanced age, the majority of individuals had crescentic GN, whereas only 15% had MN. IgA nephropathy and lupus nephritis were uncommon in all series.<sup>12</sup> Even in the very old, 40% had a treatable entity identified, and in the remainder, prognostic information was attained and potentially harmful empiric therapy was avoided. Elderly persons who are treated respond similarly to younger individuals. All published studies of biopsy in

elderly subjects show a low rate of complications and identification of treatable forms of kidney disease; however, rates of biopsy in elderly individuals continue to be low. This raises the possibility that more biopsies should be done in elderly persons. Indications for renal biopsy are shown in Table 1.

## POSTINFECTIOUS GLOMERULONEPHRITIS

The most common organism associated with acute proliferative glomerulonephritis is Group A streptococcus. This entity is uncommon in adults, and in general, its incidence is declining in the developed world. A recent review<sup>13</sup> of 86 cases showed a mean age of 56 yr, with 34% being over the age of 64. Unlike what occurs in children, as many as 38% had an underlying disorder associated with immunocompromise. Complete remission occurred in slightly more than one half of all patients and was less likely in those with pre-existing renal disease or illnesses associated with immunocompromise. Among individuals with pre-existing diabetic glomerulosclerosis, remission was rare and rapid progression to end-stage kidney disease (ESKD) often followed. Thus, outcomes seem to be worse in elderly persons.

No studies have addressed the incidence or outcomes in older individuals with postinfectious GN caused by organisms other than Group A streptococcus. Given the frequency of pneumococcal pneumonia and other infections in elderly individuals, infections that are associated with postinfectious GN less often in younger individuals may contribute a higher proportion in elderly persons.

## LUPUS NEPHRITIS

Lupus is generally a disease of women of child-bearing age; however, 10 to 20% occurs in older individuals including those over the age of 65. Arthritis, fever, serositis, sicca symptoms, Raynaud's syndrome, lung disease, and neuropsychiatric symptoms are more common in elderly patients, whereas malar rash, discoid lupus, and GN are less common. Serologic manifestations include ANA, anti-Ro, and anti-La, whereas anti-DNA is less common. When lupus with or without nephritis occurs in elderly individuals, diagnosis is often delayed. When present, lupus nephritis should be treated the same as in younger subjects.<sup>14</sup>

**Table 1.** Indications for consideration of renal biopsy in the elderly

GFR reduced to a degree greater than predicted for age alone
Acute change in GFR
Proteinuria
Active urinary sediment

## MINIMAL CHANGE DISEASE

As many as 15 to 20% of older individuals with nephrotic syndrome will have MCD.<sup>10,11</sup> Their response to treatment is comparable to younger age groups; thus, they should be treated. Risk for development of diabetes and infection is somewhat greater in elderly than in younger individuals, but untreated individuals of all ages have a high rate of infection-associated death. Among adults with nephrotic syndrome, MCD disease occurs more often in the elderly than younger adults, and in this age group, it is often misdiagnosed as congestive heart failure.

## FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS

Current evidence shows that this pathologic pattern is a heterogeneous group of diseases, and focal areas of scarring can occur in a variety of diseases including aging nephropathy. The idiopathic form of FSGS typically presents with proteinuria and reduced GFR in young adults, and it is likely caused by a variety of gene mutations. This form of GN is relatively uncommon in elderly persons and is not thought to result from pre-existing gene mutations; however, this has not been conclusively examined.

## MEMBRANOUS NEPHROPATHY

In adults of all ages, membranous nephropathy is the most common cause of nephrotic syndrome; however, the incidence is greatest in individuals 40 to 60 yr of age. After age 60, multiple myeloma and amyloidosis become much more common than in younger age groups, and thus, make up 15 to 20% of nephrotic syndrome in older individuals. Because MCD is similarly more common in elderly than younger adults, membranous nephropathy accounts for only 15% of elderly individuals with nephrotic syndrome. Treatment approaches and outcomes are similar in older and younger individuals.<sup>15</sup> Although the incidence of cancer increases with age, there is no evidence that MN and cancer are linked in elderly persons other than by coincidence.

## CRESCENTIC GLOMERULONEPHRITIS

Pauci-immune, MPO-ANCA positive, crescentic glomerulonephritis is the most common form of GN in elderly persons, and its incidence steadily increases with increasing age. Untreated, this form of GN progresses rapidly to ESKD. Differences in the forms of vasculitis and implications for therapy were recently reviewed by Jennette and Falk.<sup>16</sup> Individuals with this disease can have a significant and sustained remission with appropriate therapy; thus, recognition of this disorder in elderly individuals, with prompt biopsy and treatment, is critical

to improved outcomes. Delays in diagnosis and initiation of therapy are uniformly associated with poor outcomes; thus, recognition of this cause of acute change in renal function in contrast to other forms of acute kidney injury is essential. In all studies reported, this form of crescentic GN is the only one that is relatively unique to elderly persons. Many studies have documented changes in immune function with age, particularly in innate immunity<sup>17</sup>; however, these alone have not provided insights into the unique risk that elderly individuals have for developing this form of GN.

## MANAGEMENT OF NEPHROTIC SYNDROME IN ELDERLY PERSONS

The most important first step in the management of nephrotic syndrome in elderly persons is to recognize that edema, shortness of breath, and cardiomegaly are caused by nephrotic syndrome rather than congestive heart failure. Once the etiology of nephrotic syndrome has been defined, this should be the primary guide for therapy.<sup>18</sup> Older individuals may be sensitive to diuretics and develop prerenal azotemia; thus, they require cautious dosing and careful follow-up.

## USE OF IMMUNOSUPPRESSIVE AGENTS IN ELDERLY PERSONS

With aging, fat as a proportion of lean body mass increases, and hepatic clearance and renal function diminish. Each of these factors influences drug pharmacokinetics; thus, drug doses may need to be adjusted in elderly persons. Although there are no data specifically looking at outcomes or modified therapies in elderly individuals *per se*, most treatment studies indicate that elderly persons fair favorably compared with younger age groups in frequency of response rates and complications. Based on limited data, recommendations are to select and tailor therapy in the elderly using the same criteria as for younger individuals. Preserving renal function even when the risk of progression to ESKD is not a concern will facilitate treatment of and reduce side effects and complications of all other health related issues in the elderly.

## CONCLUSIONS

Although GN is relatively uncommon in elderly individuals, it does occur. Because treatment response rates and complications are comparable for individuals in all age groups, elderly persons will benefit from diagnosis and treatment using the same criteria for biopsy and intervention as in younger individuals. This recommendation is particularly justified given that ANCA-positive, pauci-immune, crescentic GN is the most common form of GN in elderly individuals, and left untreated, this disease rapidly leads to ESKD. Furthermore, following

progression to ESKD, outcomes in elderly persons are quite poor; thus, interventions that slow the rate of progression are of particular benefit. To improve outcomes in elderly persons, more studies that include elderly subjects are needed. To achieve this goal, biases that exclude elderly subjects from standard care and research protocols need to be modified.

## TAKE HOME POINTS

- Aging nephropathy contributes to increased risk for cardiovascular disease and frailty
- Proteinuria and sudden changes in GFR indicate the presence of kidney disease
- Elderly persons should be evaluated and treated using the same criteria as in younger individuals
- Pauci-immune, crescentic GN is a disease of elderly persons

## DISCLOSURES

None.

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## REVIEW QUESTIONS: GLOMERULAR DISEASE IN THE ELDERLY

- 1A. An 85-yr-old man is seen with complaints of joint pains caused by osteoarthritis. Before starting an NSAID, you measure his creatinine. It is 1.2 mg/dl. His estimated GFR is:
- 100 ml/min
  - 75 ml/min
  - 45 ml/min
  - 25 ml/min
- 1B. Is his eGFR equal to or different from what you expect would based on his age alone?
- Equal to
  - Better than
  - Worse than
2. Proteinuria is a normal consequence of the aging process?
- True
  - False
- 3A. A male person presents with a 4-wk history of progressive ankle and periorbital edema. Urinalysis reveals 4+ protein and no blood.  $S_{Cr}$  is 1.2 mg/dl. Which of the following is the most likely diagnosis if the individual is 10 yr old?
- Minimal change disease
  - Membranous nephropathy
  - Lupus nephritis
  - Amyloidosis
  - Focal and segmental glomerulosclerosis
- 3B. Which of the following is the most likely diagnosis if the individual is 45 yr old?
- Minimal change disease
  - Membranous nephropathy
  - Lupus nephritis
  - Amyloidosis
  - Focal and segmental glomerulosclerosis
- 3C. Which of the following is the most likely diagnosis if the individual is 80 yr old?
- Minimal change disease
  - Membranous nephropathy
  - Lupus nephritis
  - Amyloidosis
  - Focal and segmental glomerulosclerosis
- 4A. A female presents complaining of increasing fatigue, slight ankle edema, headaches, dark colored urine, and morning nausea of 3-wk duration. Urinalysis reveals 2+ protein, 3+ blood, granular, and red cell casts.  $S_{Cr}$  is 2.6 mg/dl. If she is 8 yr old, which of the following is the most likely diagnosis?
- Pauci-immune crescentic glomerulonephritis
  - Postinfectious glomerulonephritis
  - Lupus nephritis
  - Acute cystitis
  - Membranous nephropathy
- 4B. If she is 24 yr old, which of the following is the most likely diagnosis?
- Pauci-immune crescentic glomerulonephritis
  - Postinfectious glomerulonephritis
  - Lupus nephritis
  - Acute cystitis
  - Membranous nephropathy
- 4C. If she is 83 yr old, which of the following is the most likely diagnosis?
- Pauci-immune crescentic glomerulonephritis
  - Postinfectious glomerulonephritis
  - Lupus nephritis
  - Acute cystitis
  - Membranous nephropathy
5. Treatment responses in individuals with glomerulonephritis are dependent on diagnosis and therapy. These principles of treatment and the response rates are comparable in elderly and younger individuals.
- True
  - False