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**Primary glomerular diseases in the elderly**

Sumnu A *et al*. Glomerular diseases in the elderly

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**Abstract**

Primary glomerular diseases in the elderly population are a frustrating topic due to difficulties in both the diagnosis and decision making about treatment. The most frequent type of primary glomerular disease in elderly is membranous nephropathy; while its counterpart in younger population is IgA nephropathy. The most frequent cause of nephrotic syndrome in the elderly is also membranous nephropathy. Pauci-immune crescentic GN rate increases both in elderly and very elderly population. Pauci-immune crescentic GNs should be regarded as urgencies in elderly patients as in their younger counterparts due to potential for causing ESRD in case of delayed diagnosis and treatment, and also causing mortality due to alveolar hemorrhage in patients with pulmonary involvement. Renal biopsy is the inevitable diagnostic method in the elderly as in all other age groups. Renal biopsy prevents unnecessary treatments and provides prognostic data. So advanced age should not be the sole contraindication for renal biopsy. The course of primary glomerular diseases may differ in the elderly population. AKI is more frequent in the course and renal functions may be worse at presentation. These patients are more prone to be hypertensive. The decision about adding immune suppressive therapies to conservative methods should be made considering many factors like co-morbidities, drug side effects and potential drug interactions, risk of infection, patient preference, life expectancy and renal functions at the time of diagnosis.

**Key words:** Elderly; Membranous nephropathy; Pauci-immune crescentic glomerulonephritis; Primary glomerular disease; Renal biopsy

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**Core tip:** Primary glomerular diseases in the elderly population are a frustrating topic due to difficulties in both diagnosis and treatment. The most frequent type of primary glomerular disease and the most frequent cause of nephrotic syndrome is membranous nephropathy. The frequency of pauci-immune glomerulonephritides increases considerably in the very elderly population. Renal biopsy is the inevitable diagnostic method in the elderly as in all other age groups. The decision about adding immune suppressive therapies to conservative methods should be made considering many factors like co-morbidities, drug side effects, patient preference, life expectancy and renal functions at the time of diagnosis.

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**INTRODUCTION**

Primary glomerular diseases (PGD) in the elderly deserves mention under a heading separate from PGDs in young adults due to differences in epidemiological and clinical characteristics, and difficulties in diagnosis and decision making about diagnosis. Co-morbidities, shorter life expectancy, complications of renal biopsy and immunosuppressive medications are among the factors that challenge the clinicians about diagnosis and treatment. Paucity of clinical studies and so insufficiency of evidence and guidelines are other problems in the elderly population that increases progressively due to increased mean life expectancy[1]. First, general epidemiological and clinical characteristics of PGDs in the elderly will be mentioned followed by details about specific diseases.

The frequency of PGDs in the elderly may change in countries. Ethnic predisposition, different approaches about biopsy indications and differences in the methods and design of epidemiological studies are among the causes of this variability. We learn about epidemiological data about PGDs in the elderly, from glomerulonephritis or biopsy registries of countries. These studies may be classified as involving ‘elderly’ (> 60-65 years) and ‘very elderly’ (> 80-85 years) patients,

Some of the registries that you can gain information about epidemiological data in the elderly population in Europe are those of Italy, Spain, Czech Republic and Turkey[2-5]. Membranous nephropathy (MN) was reported in these studies as the most frequent PGD and the most frequent cause of nephrotic syndrome in patient older than 65 years. The PGD in the second order changes in different countries. The evaluation of pauci-immune crescentic glomerulonephritis (pauci-immune crescentic GN) within PGDs in some studies while within secondary glomerular diseases in the others leads to difficulties in evaluation of epidemiological studies. The most frequent biopsy indication is nephrotic syndrome as expected whether accompanied by acute kidney injury (AKI) or not. The manuscript by Yokoyama *et al*[6] who presented data of Japan Renal Biopsy Registry has a special place in the literature due the highest number of patients. Data of 2802 patients aged > 65 (Group A) and 276 patients aged > 80 years (Group B) were presented in this study. 45% of cases were PGDs. The most frequent PGDs in Group A and B were MN, IgA nephropathy (IgAN) and minimal change disease (MCD) in order, while the most frequent diagnoses in elderly patients who had renal biopsy due to nephrotic syndrome were MN, MCD and focal segmental glomerulosclerosis (FSGS) with decreasing order. The most frequent biopsy indication was nephrotic syndrome in both groups, while rapidly progressive glomerulonephritis (RPGN) was the second most frequent cause in Group B. When compared with patients aged less than 65 years, pauci-immune crescentic GN, MN, type 1 and 3 membranoproliferative glomerulonephritis (MPGN) were more frequent and IgAN was significantly less frequent in patients aged more than 65 years. The ratio of renal biopsies performed due to RPGN was higher in the elderly population compared to younger counterparts. There are also current studies presenting epidemiological data of elderly patients in a single center besides registry studies[7-10]. MN was again the most frequent diagnosis in these studies except in the study by Brown *et al*[10] in which pauci-immune crescentic GN was the most frequent PGD. Recent studies about the epidemiology of PGD in elderly are summarized in Table 1.

Recent articles have been published about epidemiological data of very elderly patients although the age limit is variable [11-15]. Although all cases are not PGDs in these studies, they provide important information about PGDs in the very elderly population. The most frequent PGD in studies originating from United States[11,14] was pauci-immune crescentic GN, while it was MN in other studies from European and Asian countries. Biopsy indications in these studies follow the same order, and provide clues about behavior regarding biopsy indication in this special age group in these countries. The most frequent biopsy indication is AKI in United States, while it is nephrotic syndrome in other European and Asian countries. Studies performed with very elderly patients are summarized in Table 2.

Although renal biopsy is the inevitable diagnostic method in glomerular diseases, it is not performed in some of the patients due to various factors including co-existing systemic diseases, shorter life expectancy, reluctance of the clinicians about biopsy and immunosuppressive treatment and patient preference. There are studies in the literature reporting that bleeding risk after renal biopsy in elderly patients is not different from other age groups[16,17].But, the possibility that clinicians would have performed renal biopsy in elderly patients with lower risk in these studies in which data of biopsy series are presented, should be kept in mind. As well known, the most important predictor of bleeding complication is serum creatinine level[17]. This complication is more common in patients with renal failure compared to patients without. The concern of clinicians about this complication is not undue considering physiological changes related to age, co-existing systemic diseases (hypertension, atherosclerosis, diabetes mellitus, amyloidosis), and overestimation of glomerular filtration rate with creatinine level due to decreased muscle mass. When possible complications of immunosuppressive treatment add on these concerns, some clinicians prefer conservative methods without performing renal biopsy. Some other clinicians on the other hand try empiric immunosuppressive treatment without biopsy. Yoon *et al*[18] evaluated this subject in their study. They evaluated renal and patient survival rates of 99 patients (age > 60 years) presenting with nephrotic syndrome who were grouped as those who had renal biopsy (*n* = 64) and those who did not (*n* = 35). The major defect of this study was the lower mean age and better renal functions in the group who had renal biopsy. Although complete remission was more frequent (45% *vs* 26%, *P* = 0.013) in the biopsy group in which statistically significantly more patients had immunosuppressive therapy (*P* < 0.005), renal survival rates were similar. Patient survival was lower in the group without biopsy which was not a surprise considering significantly higher mean age.

On the other hand, there are factors that lead the clinician towards biopsy like need of urgent diagnosis for optimum treatment of pauci-immune glomerulonephritides presenting as RPGN; the risk of not giving specific treatment considering more susceptibility of elderly to infective and thrombotic complications of nephrotic syndrome[19,20]; prevention of unnecessary treatments by renal biopsy; and provision of prognostic data. Studies with very elderly patients revealed that therapeutic approach may change 40%-67% with renal biopsy[11,14]. So, advanced age should not be the sole contraindication for renal biopsy. The clinician has to decide respecting the preference of the patient within this multifactorial equation.

Renal biopsy in elderly has the potential to be problematic for pathologists as well as clinicians. Varying degrees of ‘background’ glomerulosclerosis, tubular atrophy, arteriolar hyalinosis that may be seen as a result of both senility and co-morbidities may superimpose primary and secondary glomerular diseases[21].

Primary glomerular diseases in the elderly present as nephrotic syndrome, nephritic syndrome, RPGN, asymptomatic urine abnormalities or chronic glomerulonephritis as in other age groups. But nephrotic syndrome and acute nephritic syndrome including RPGN comprises most of the cases as can be understood from biopsy indications in reported by biopsy series. PGDs causing nephrotic syndrome are MN, FSGS and MDH, while MPGN, IgAN and pauci-immune crescentic GNs comprise the major causes of nephritic syndrome. But different and complex forms of presentation are not rare. As an example, AKI superimposed on nephrotic syndrome is more frequent in elderly population.Some of the authors consider AKI on the basis of nephrotic syndrome as idiopathic if there is no clear reason as drug use, exposure to radio contrast agent or interstitial nephritis[22].

The treatment of PGDs in the elderly causes difficulties as the diagnosis. Co-morbidities, the number of pills that the patients take, potential drug interactions, risk of infection, patient preference, expected life expectancy, renal functions at the time of diagnosis, increased drug toxicity risk due to age related decreased in drug metabolism and excretion[23,24] are some of the factors effective on the decision of the clinician about treatment. Moreover, disease specific secondary causes should be searched for promptly as well as any contraindication for treatment and screening for malignancy appropriate for the age group should be performed.

Conservative methods are the sine qua non of treatment of patients with nephrotic syndrome in this age group. Salt restriction, smoking cessation, diuretics, renin-angiotensin-aldosterone system blockers, statins, anticoagulant agents and pneumococcal vaccination are the components of conservative treatment[25,26]. Anticoagulation is recommended in patients with serum albumin level below 2 g/dl and co-existing risk factors if bleeding risk not high. But treatment decision should be individualized as in all cases. An article reporting the importance of forming a scaling system for thrombosis and bleeding before decision about anticoagulant use has been published recently[27].

Immunosuppressive therapy should be considered in cases with nephrotic proteinuria in spite of conservative methods, progressively declining renal functions, life threatening complications of nephrotic syndrome like thrombosis, and patients with RPGN. No guideline has been developed up to now for glomerulonephritides in the elderly. ‘KDIGO (Kidney Disease Improving Global Outcomes) Clinical Practice Guideline for Glomerulonephritis’ published in 2012 helps the clinicians caring elderly patients. But it is difficult to adopt all recommendations to old patients. The clinician has to choose the correct treatment method considering both positive and negative sides together. All medications should be used in doses appropriate for the renal function of the patient.

**MEMBRANOUS NEPHROPATHY**

The most frequent PGD in adult population all over the world is IgAN as is well known[28,29]. But MN with its frequency increasing with aging, is the most common PGD and the most common reason of nephrotic syndrome in elderly. AKI is more frequent in the course of disease compared to other PGDs. Advanced age has been reported to be a risk factor for AKI in patients with MN[30]. Moreover, hypertension and worse renal functions at the time of presentation are expected to be more prevalent in elderly patients. There are studies reporting increased risk of thrombotic[31] and infectious[32] complications compared to adult patients.

The PGD that is most associated with malignancies is MN, and it is speculated that it accompanies tumors in 10% of cases[33,34]. M type anti phospholipase A2 antibodies that started a new era protects from unnecessary interventional investigations[35,36]. There is a tendency to screen patients with M type anti phospholipase A2 antibodies in accordance with age; while more complicated screening is necessary in those without anti phospholipase A2 antibody[37]. Another difference is in the subtypes of IgG on immune fluorescent microscopy, although not routinely studied. IgG4 predominates in primary MN, while IgG1 and/or IgG2 staining is expected to be positive in MN associated with malignancies[36]. Malignancies are usually clinically evident at the time of diagnosis of nephrotic syndrome. However, there are reported cases with malignancies reported late in the course. Some authors think that screening for cancer should be repeated within 5-10 years in cases with histological and serological testing resembling secondary MN[38,39]. History of medications, screening for infection (hepatitis B and malaria) and evaluation for systemic lupus erythematosus should not be forgotten. Nonsteroidal anti-inflammatory drugs (NSAID) are in the first order among drugs related with MN. NSAIDs may cause MN and MDH as well as non-glomerular diseases[40,41].

It has been shown that corticosteroid therapy alone in elderly patients with MN is not enough and actually, it is related with more complication[42,43]. Ponticelli protocol (in which steroids are used in combination with either chlorambucil or cyclophosphamide) can be tried[44]. KDIGO guideline proposes immunosuppressive treatment in patients with severe life-threatening symptoms and findings, proteinuria more than 4 g/d in spite of conservative methods, or at least 30% increase in serum creatinin level within the last 6-12 mo[26]. However, there are no up-to-date randomized controlled trials about side effect profile and efficacy of steroid treatment in old patients. Besides, studies about the role of cyclosporine plus low dose steroid, and mycophenolate mofetil are not enough also. We can mention a study in which mizoribin was used in a few old patients. But the number of patients is not enough, and mizoribin group was not compared with patients receiving only steroid treatment[45].

**MINIMAL CHANGE DISEASE**

Minimal change disease which is one of the important causes of nephrotic syndrome in elderly presents withy hypertension and AKI more compared with younger population. Some authors believe that AKI superimposed on nephrotic syndrome in elderly is commonly associated with MCD, and elderly patients are more prone to acute tubular necrosis[46,47]. Relapses are rarer in patients older than 40 years compared to patients younger than 40 years[47,48]. All immunosuppressive medications used in the treatment of glomerulonephritis have been tried with considerable success, although steroids remain to be the mainstay of treatment[26].

**FOCAL SEGMENTAL GLOMERULOSCLEROSIS**

We do not have enough data in the literature about the clinical characteristics and treatment of FSGF in the elderly. Tip variant of FSGS has been reported to be the histologic type presenting with sudden onset of severe nephrotic syndrome and also the type which is the most sensitive to steroid treatment. Tip lesions ten de be more prevalent in older patients[49,50]. Important predictors of renal prognosis are the magnitude of proteinuria, the level of kidney function, and the amount of tubulointerstitial injury[51]. Corticosteroids are the first line treatment in appropriate patients while second line treatment with cyclosporine plus low dose steroid may be preferred in cases for which there is considerable risk for corticosteroid side effects [26]. Evaluation for secondary causes of FSGS should not be omitted. Interferons[52] and intravenous use of bisphosphonates (especially pamidronate)[53] which are commonly prescribed in this population are examples for causes of secondary FSGS. American Society of Clinical Oncology published an update for use of bisphosphonates in multiple myeloma including knowledge about dose reduction in case of decreased renal function[54].

**IGA NEPHROPATHY**

IgA nephropathy is associated with more severe renal manifestations at presentation in the elderly. It has been reported in Spanish Registry of Glomerulonephritis that 27.8% of patients with IgAN older than 65 years presented as AKI[3]. This ratio reached to 53% in another study with the emphasis that tubular injury is more prominent than glomerular damage in these patients[55]. Advanced age has been determines as a risk factor for progression to end-stage renal disease (ESRD) which was found to be 1.95 times more common compared to young adults[56]. An article has been published recently reporting that 70% of patients reach ESRD within 20 years [57]. The only immunosuppressive medication proved to be effective in IgAN is corticosteroids. Although persistent proteinuria in spite of conservative measures is an indication for corticosteroid treatment according to KDIGO guideline, it may not be wise to give corticosteroid treatment to elderly patients with normal renal functions, blood pressure and non-nephrotic range proteinuria, especially in the presence of comorbidities. However, IgAN presenting as crescentic glomerulonephritis should be treated as pauci-immune crescentic glomerulonephritis[26].

**MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS**

Primary MGPN is a rare disease. So, secondary causes, especially monoclonal gammopathies and hepatitis C infection, should be ruled out case of pathological diagnosis of MPGN[58,59]. Although usually not responsive, corticosteroid+mycophenolate mofetil or corticosteroid+oral cyclophosphamide may be tried in patients with MPGN type I presenting with nephrotic syndrome and/or rapid increase in creatinine levels[26,60]. But patients and relatives should be informed thoroughly about the low response rates before deciding for immunosuppressive treatment.

**PAUCI-IMMUNE CRESCENTIC GLOMERULONEPHRITIS**

Pauci-immune crescentic GN is disease group with increased rate both in elderly and very elderly population[61]. This group represents renal involvement in anti-glomerular basement membrane disease and anti-neutrophil cytoplasmic autoantibody associated vasculitides. Renopulmonary syndrome is the more frequent type of presentation although isolated renal involvement may also be seen. The first explanation for increased frequency is the peak that the systemic vasculitides show between ages 65-74 years [62]. Moreover, presentation with RPGN increases the probability of performing renal biopsy in these patients for whom the clinicians may prefer to remain conservative otherwise. Pauci-immune crescentic GNs should be regarded as urgencies in elderly patients as in their younger counterparts due to potential for causing ESRD in case of delayed diagnosis and treatment, and also causing mortality due to alveolar hemorrhage in patients with pulmonary involvement[63]. Renal biopsy should be scheduled immediately and serum samples should be taken for determination of anti-neutrophilic cytoplasmic antibody, anti-glomerular basal membrane antibody and then immunosuppressive treatment should be started as soon as possible. In the absence of absolute contraindications, pulse corticosteroid and cyclophosphamide treatment should be started together with plasma exchange in the presence of alveolar hemorrhage or rapid decline in renal functions[26]. In case of vasculitides limited to kidney, decision about treatment and its duration should be made regarding comorbidities and activity/chronicity of lesions on renal biopsy. Renal survival in anti-glomerular basal membrane disease is related with creatinine levels at the time of admission[64]. So, early diagnosis and treatment have prime importance. Independent determinants of mortality in anti neutrophil cytoplasmic autoantibody-associated vasculitides have been found to be advanced age and pulmonary infections[65]. KDIGO guideline recommends crescentic forms of any PGDs to be considered as pauci-immune GN and treated so[26].

As a conclusion, PGDs in elderly are a group of diseases that challenges the clinicians in both diagnosis and treatment. Although MN is the most common PGD in this age group, crescentic glomerulonephritides should always be considered due to irretrievable results.

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**Table 1** **Recent epidemiological studies in the elderly**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Country** | **Ref.** | **Date** | **Number of cases** | **Age** | **The Most frequent PGDs** |
| Italy1  | Vendemia *et al*[2] | 2001 | 280 | > 65 | 1. MN2. Pauci-immune GN3. MPGN |
| Turkey[5]  | Öztürk *et al*[5] | 2014 | 150 | > 60 | 1. MN2. Pauci-immune GN3. FSGS |
| Japan  | Yokoyama *et al*[6] | 2012 | 2802 | > 65 | 1. MN2. IgAN3. MCD |
| Brasil | Carmo *et al*[7] | 2010 | 113 | > 60 | 1. MN2. FSGS3. MCD |
| South Africa  | Okpechi *et al*[8] | 2013 | 111 | > 60 | 1. MN2. IgAN3. Pauci-immune GN |
| China | Jin *et al*[9] | 2014 | 851 | > 65 | 1. MN2. IgAN3. MCD |
| Ireland | Brown *et al*[10] | 2012 | 236 | > 65 | 1. Pauci-immune GN2. MN3. IgAN |

1Only patients with PGDs were included in this study, while other studies included patients with secondary glomerular diseases also. FSGS: Focal segmental glomerulosclerosis; GN: Glomerulonephritis; IgAN: IgA nephropathy; MCD: Minimal change disease; MN: Membranous nephropathy; MPGN: Membranoproliferative glomerulonephritis; PGD: Primary glomerular disease.

**Table 2** **Recent epidemiological studies in the very elderly population**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Country** | **Ref.** | **Date** | **Number of cases** |  **Age** | **The most frequent PGD** |
| Japonya | Yokoyama *et al*[6] | 2012 | 276 | > 80 | 1. MN2. IgAN3. MCD |
| United States | Moutzouris *et al*[11] | 2009 | 235 | > 80 | 1. Pauci-immune GN2. MN3. IgAN |
| Italy | Rollino *et al*[12] | 2014 | 131 | > 75 | 1. MN2. Pauci-immune GN3. IgAN |
| Japan | Omokawa *et al*[13] | 2012 | 73 | > 80 | 1. MN2. MCD |
| United States | Nair *et al*[14] | 2004 | 100 | > 80 | 1. Pauci-immune GN2. MN |
| Spain  | Verde *et al*[15] | 2012 | 71 | > 85 | 1. MN2. Pauci-immune GN3. IgAN |

|  |
| --- |
| FSGS: Focal segmental glomerulosclerosis; GN: Glomerulonephritis; IgAN: IgA nephropathy; MCD: Minimal change disease; MN: Membranous nephropathy; MPGN: Membranoproliferative glomerulonephritis; PGD: Primary glomerular disease.  |