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Spectrum of Biopsy-Proven Kidney Diseases in Older Saudi Adults, 2001-2017

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Abstract

Introduction: Glomerular diseases in the elderly population are a challenging clinical dilemma, and kidney biopsy is of paramount importance to clarify the morphological changes. The aim of this study was to evaluate the prevalence of major glomerulopathies that affect older adults.

Methods: This retrospective study included 70 adults aged >65 years and was performed at four tertiary centres in Saudi Arabia between January 2001 and December 2017.

Results: There were 74 native kidney biopsies, which accounted for 7.2% of all native renal biopsies that were performed in the 16-year period. Furthermore, 64% of the native biopsied patients were men. The most common clinical presentations were nephrotic syndrome (40%) and acute kidney injury (20%).

In older adults with primary glomerular diseases, IgA nephropathy was the most frequent pathological type (36.4%), whereas diabetes mellitus was the most frequent etiology (37.5%) for secondary glomerular diseases. Women were more likely to develop diabetic nephropathy.

Conclusion: The prevalence of IgA is progressively increasing and is currently the most frequent type of primary glomerular disease diagnosed in senior adult. Diabetes has become the leading cause of secondary glomerular disease. Renal biopsy is therefore of paramount importance because an accurate diagnosis will help clinicians establish the diagnosis and guide therapy for both younger and older adults.

Keywords: Glomerulonephritis; Kidney biopsy; Senior adult

Introduction

Life expectancy has increased worldwide, with an average life expectancy of 74.8 years in Saudi Arabia [1]. This has a major impact on the management of all diseases, including glomerular diseases (GN). Most of the GN studies either exclude or under represent senior adults (i.e., those aged >65 years). The prevalence and natural course of common glomerular disease in young adults are not necessarily applicable to senior adults. New research should focus in this rapidly growing section of the community.

Studies evaluating the frequency of specific types of GN in different geographical locations revealed differences in frequency that may be attributable to ethnicity, genetic predisposition, or environmental factors [2,3]. With the improvement in health care services and socioeconomics, the incidence of some risk factors can change, which may lead to a change in the incidence of some of glomerular disease subtypes patterns, including diabetic glomerulosclerosis and secondary GN [2]. Although the numbers of studies that have examined various kidney biopsy findings are limited, different patterns have emerged based on the region of the study [4-8]. We are not aware of any published studies examining the pattern of glomerular diseases in older Saudi adults. The aim of this study is to examine the change in various diseased kidney biopsies in Saudi Arabia alongside the change in incidence of different glomerular disease over the last 16 years.

Method

In this retrospective observational study, we included all patients over 65 years with a native renal biopsy performed

during a 16 year period (from January 2001 to December 2017) at 4 tertiary hospitals in Saudi Arabia. These hospitals were King Khalid University Hospital in Riyadh, Security Forces Hospital in Riyadh, King Abdulaziz National Guard Hospital in Riyadh, and King Abdulaziz University Hospital in Jeddah. Demographic and clinical data of each patient at the time of renal biopsy were collected and these included: age, gender, clinical presentation, indication for renal biopsy (nephrotic syndrome, nephrotic range proteinuria, acute nephritic syndrome (ANS), rapidly progressive glomerulonephritis (RPGN) syndrome, chronic nephritic syndrome, asymptomatic haematuria with proteinuria, and AKI), urine analysis, serum creatinine level, serum albumin level, 24-h urine protein level, and/or protein/creatinine ratio.

Percutaneous renal biopsies were performed in all patients and examined using light microscopy, immunofluorescence and electron microscopy, by specialized renal pathologists. The histologic findings were classified into two major classes: (1) primary glomerulonephritis, including minimal change disease, IgA nephropathy, membranous, membranoproliferative, and focal segmental glomerulosclerosis (FSGS), and (2) secondary glomerulonephritis, including lupus nephritis, diabetes, systemic vasculitis, amyloidosis, and myeloma-associated glomerulonephritis. During this period, a total of 74 native renal biopsies were performed. Incomplete records (n=4) were excluded, and a total of 70 cases were enrolled in the study.

The research was performed in compliance with the Declaration of Helsinki and was approved by the ethics committee of King Khalid University Hospital (E12-811).

Statistical analysis

Statistical analysis was performed using the SAS software. Categorical variables are reported as absolute number and percentage, and the continuous variables are given as the median or mean with standard deviation. When analysing different glomerular disease across gender, P values for trends were reported. Differences in frequencies of various glomerular diseases among male and female patients were compared using the chi-square test/Fisher's exact test. $P \leq 0.05$ was considered significant.

Results

The study included 70 cases with the mean age at time of kidney biopsy were 72.9 ± 6.3 years. The total numbers of elderly patients receiving renal biopsy increased yearly as the majority of cases (80%) were performed after 2010. The patients receiving renal biopsy were predominantly male (**Table 1**).

The median serum creatinine level was 245 µmol/l with a median daily urine protein level of 2.9 g/day and 6 (8.6%) patients required dialysis on their initial presentation (**Table 1**). The most common indications for kidney biopsy were nephrotic syndrome (40%) and acute kidney injury (20%).

Secondary GN accounted for the majority of the cases in 48.6%, with primary GN accounting for 37.1%, and tubulointerstitial diseases was observed in 2.9% of cases (**Figure 1**).

Table 1: Demographic and indication for kidney biopsy of 70 adult who underwent kidney biopsy in from 2001 to 2017.

Total number of patients	**70**
Gender, n (%)	
Male	45 (64.3)
Female	25 (35.7)
Age at biopsy, years (mean)	72.9 ± 6.3
Serum creatinine, mean µmol/l (median)	295 ± 223 (245)
Serum albumin, mean gm/l, (median)	25.6 ± 6.9 (26)
Urine protein, mean in gm/day (median)	4.1 ± 4.2 (2.9)
Indication for renal biopsy, n (%)	
Nephrotic syndrome	28 (40)
Nephritic syndrome	10 (14.3)
Renal impairment	14 (20)
Hematuria	9 (12.9)
Sub-nephrotic proteinuria	9 (12.9)

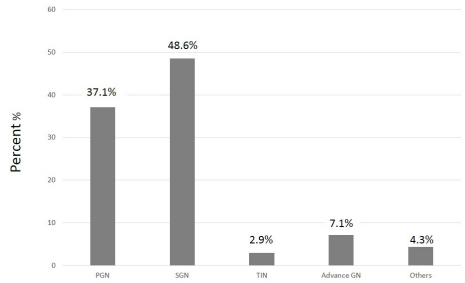

Figure 1: The distribution of histological diagnosis as determined by kidney biopsy among 70 Saudi older adults underwent renal biopsy from 2001 to 2017. Frequencies of the main groups shown as a proportion of the whole cohort. PGN: Primary Glomerular Disease; SGN: Secondary Glomerular Disease; TIN: Tubulointerstitial Diseases; Advance GN: Advance Glomerular Disease.

Among primary GNs, IgA nephropathy (36.4.0%), FSGS (27.3%), and membranous (22.7%) were the most frequent diagnoses (**Table 2**). In contrast, diabetic nephropathy (68.6%) and amyloidosis (8.3%) were the most common causes of secondary glomerular diseases (**Table 3**). ANCA/pauci-immune GN was noted in 8.3% of the cases.

Table 2: Histological diagnosis of primary glomerular diseases among 70 older adults who underwent kidney biopsy in Saudi Arabia from 2001 to 2017.

Glomerular disease subtype	Number (%)
IgAN	8 (36.4)
FSGS	6 (27.3)
MEM	5 (22.7)
MPGN	2 (9.1)
MCD	1 (4.5)

Frequencies of the different subtypes shown as a proportion of the primary glomerular disease cohort. IgAN: IgA Nephropathy; MPGN: Membranoproliferative; MCD: Minimal Change Disease; FSGS: Focal Segmental Glomerulosclerosis; MEM: Membranous Nephropathy

Table 3: Histological diagnosis of secondary glomerular diseases among 70 older adults who underwent kidney biopsy in Saudi Arabia from 2001 to 2017.

Glomerular disease subtype	Number (%)
Diabetes mellitus, n (%)	18 (37.5)
Lupus nephritis, n (%)	3 (6.3)
Amyloidosis, n (%)	4 (8.3)
ANCA, n (%)	3 (6.3)
Post infectious GN, n (%)	2 (4.2)
HUS/TTP, n (%)	2 (4.2)
Anti-GBM, n (%)	1 (2.1)
Viral hepatitis associated, n (%)	2 (4.2)
Acute interstitial nephritis, n (%)	2 (4.2)
Advanced GN, n (%)	5 (10.4)
Others, n (%)	6 (12.5)

GN: Glomerulonephritis; ANCA: Antineutrophil Cytoplasmic antibodies: Anti-GBM: Anti-Glomerular Basement Membrane; TTP: Thrombotic Thrombocytopenic Purpura; HUS: Hemolytic-uremic Syndrome. Frequencies of the different subtypes shown as a proportion of the all kidney biopsies cohort

Among the four most common primary GNs (IgA, FSGS, MCD and MEM), male predominance was found with 44% male *vs.* 24% female (P=0.08). Secondary GN was reported in 35.6% *vs.* 68% in men *vs.* women, respectively (P=0.01). DM was significantly higher in females than in males and accounted for 44% and 20%, respectively, (P=0.03). IgA distributions were not significantly different between genders 3.3% in male and 8% in female (P=0.5).

Discussion

A clear understanding of the pattern of renal diseases and their evolving pattern helps clinicians to focus on the future clinical trials addressing the underling etiologies, pathogenesis and most appropriate therapies. Despite a growing proportion of elderly individuals worldwide and well-developed guidelines for management of various glomerular disease in children and adults, none of these guidelines address the correct approach needed to explore glomerular disease in older adults. Extrapolating the treatment approach for seniors from trials performed in young adults has it is own shortcomings. It is anticipated that the responses and profile of adverse effects in senior adults will differ from those in children and young adults. There are several small epidemiologic population-based studies of biopsy-proven nephropathies in Saudi; however, this the first study that examines the pattern in elderly people in Saudi that can be extrapolated to the other Gulf Cooperation Council (GCC) countries in South west Asia.

Male significantly outnumbered female among the patients who received renal biopsies, which was also reported by Jin et al. and Ping et al. [9,10]. However, in middle-aged adults, the prevalence of glomerular disease is similar between genders [11]. This probably related to the decline in the incidence of autoimmune diseases with age as many of these diseases are more prevalent in young females (for example lupus).

Globally, IgA nephropathy (IgAN) is the most common primary glomerular diseases with increasing prevalence. Although for years, the prevalence of FSGS was the commonest glomerular disease; however, our study showed that IgA is becoming the first reported primary GN in the elderly. This is possibly related to increasing IgA incidence as has been reported by other [11]. The main challenge is to understand why the IgA continue to increase and why there is an almost absence of effective therapeutic interventions.

The second important result is the diabetes in the commonest cause for secondary GN. This is despite the fact that many patients do not undergo a kidney biopsy to confirm diagnosis. The prevalence of diabetes in Saudi Arabia is one of the highest internationally, and it is not surprising that this impacts the incidence of diabetic nephropathy. Obesity is a leading risk factor for type 2 diabetes, and the prevalence of abdominal obesity for Saudi females was reported as 50-70% [12].

The third critical finding was that although hypertension has been listed as a second common cause of end-stage renal disease in both the Saudi and global populations, none of our patients showed hypertensive nephrosclerosis, although older adults are believed to be the most susceptible group [13,14]. This is can be explained by the vague definitions of disorders. Hypertensive nephrosclerosis is a vaguely defined clinical entity most commonly observed in individuals with hypertension and advanced chronic kidney disease (CKD) in the absence of other causes for renal failure. Similarly, histologically, the kidney biopsies in patients with a clinical diagnosis of hypertensive nephrosclerosis typically reveal nonspecific segmental or global glomerulosclerosis with marked interstitial fibrosis, making diagnosis difficult to ascertain in these cases. In addition, the presentation of hypertensive nephrosclerosis is often indolent with slowly progressive renal insufficiency with small amount of proteinuria that oftentimes does not prompt renal biopsy. The other potential explanation is reconsidering the role of hypertension and determining if it is an innocent bystander or a true cause of end-stage renal disease.

Our study has several limitations. The retrospective design has limited access to patient data and may suffer from selection bias. Therefore, our results need to be confirmed using larger prospective cohort studies that also look into the genetic and

demographic factors impact on glomerular disease in older Saudi. Retrospective methodologies are vulnerable to loss of information. Selection bias is also an important limitation, as many cases may not undergo a kidney biopsy which will lead to underestimation of levels of some diseases. This study has a relatively modest sample size; however, the biopsy frequencies in those older than 65 years will always continue to be a challenge. Despite these limitations, it is envisioned that eventually the management of older adults with glomerular diseases will need to be developed and examined.

Conclusion

The prevalence pattern of glomerular disease is changing, and many cases are diagnosed late when the disease has already affected kidney function. Kidney biopsy should always be considered early in the course of the diseases due to an inevitable poor outcome in the case of late therapy. Although IgA nephropathy is the most common primary glomerular disease in this age group, diabetic nephropathy is becoming the commonest secondary glomerular disease.

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