

# Prevalence and 20-year epidemiological trends of glomerular diseases in the adult Saudi population: a multicenter study

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**BACKGROUND:** Recent international reports have shown significant changes in the incidence of different glomerular diseases.

**OBJECTIVE:** Examine temporal and demographic trends of biopsy-diagnosed glomerular diseases in the adult population of Saudi Arabia over the last two decades.

**DESIGN:** Medical record review.

**SETTINGS:** Four tertiary medical centers in Saudi Arabia.

**PATIENTS AND METHODS:** We identified all patients that underwent native kidney biopsy between 1998 and 2017.

**MAIN OUTCOME MEASURES:** The frequency and the disease trends in four biopsy eras (1998-2002, 2003-2007, 2008-2011, and 2012-2017) for different glomerular diseases.

**SAMPLE SIZE AND CHARACTERISTICS:** 1070 patients, 18-65 years of age; 54.1% female.

**RESULTS:** Of 1760 patients who underwent native kidney biopsies, 1070 met inclusion criteria. Focal segmental glomerulosclerosis was the most common biopsy-diagnosed disease, with comparable frequencies over the four eras (23.6%, 19.8%, 24.1%, and 17.1, respectively [*P* value for trend=.07]). The frequency of immunoglobulin A nephropathy increased progressively. The incidence of membranoproliferative glomerulonephritis declined significantly. Among the secondary types of glomerular diseases, systemic lupus erythematosus-associated lupus nephritis was the most common, followed by diabetic nephropathy. The prevalence of diabetic nephropathy increased from 1.4% in the first era to 10.2% in the last one.

**CONCLUSIONS:** Trends in biopsy-diagnosed glomerular disease have changed. While focal segmental glomerulosclerosis remains the most common glomerular disease, there has been a significant rise in the prevalence of immunoglobulin A nephropathy and diabetic nephropathy. In contrast, membranoproliferative glomerulonephritis has declined.

**LIMITATION:** Retrospective methodologies are vulnerable to lost data.

**CONFLICT OF INTEREST:** None.

**G**lomerular diseases are one of the major causes of end-stage kidney disease around the world.<sup>1</sup> Despite the rarity of these diseases, they can cause significant morbidity and economic burden.<sup>2</sup> A kidney biopsy is essential in establishing the diagnosis of glomerular diseases and in guiding their management.<sup>3</sup> Previous epidemiologic studies have shown varying incidences of both primary and secondary glomerular diseases across different patient age groups, ethnicities, geographical regions, and time periods.<sup>4</sup>

In the United States, focal segmental glomerulosclerosis (FSGS) is the most frequently reported primary glomerulopathy in biopsy registries,<sup>5,6</sup> whereas immunoglobulin A (IgA) nephropathy is the most common primary glomerular disease identified in kidney biopsies in European and Asian registries.<sup>2,7</sup> In contrast, a systematic review from Africa showed a low incidence of IgA nephropathy and more frequent cases of FSGS (in sub-Saharan Africa) and membranoproliferative glomerulonephritis (MPGN) (in Northern Africa) as compared to other subtypes.<sup>8</sup> In the United States, previous studies reviewing temporal trends of glomerular disease subtypes showed an increase in the incidence of FSGS over a period of three decades.<sup>9</sup> An increase in the incidence of a particular glomerular disease over time may signal an increased exposure to an environmental or behavioral factor.<sup>10</sup>

Earlier studies from Saudi Arabia described a higher prevalence of MPGN as compared to other primary glomerular disease subtypes;<sup>11,12</sup> however, recent studies report that FSGS is the most common biopsy-diagnosed glomerular disease.<sup>13-15</sup> Despite the importance of these studies in the understanding of the epidemiology of the different glomerular disease subtypes, they are mostly cross-sectional studies, reporting incidences during a specified period only. The temporal changes in incidence of the different subtypes of primary and secondary glomerular diseases have not been previously reported in Saudi Arabia. The aim of this study was to describe the changes in the pattern of different primary and secondary glomerular diseases in Saudi adults reported from five tertiary centers in the country over the past 20 years.

## PATIENTS AND METHODS

For this study, five tertiary hospitals centers took part: (1) King Saud University Medical City, Riyadh; (2) King Faisal Specialist Hospital and Research Center, Riyadh; (3) King Abdulaziz University Hospital, Jeddah; (4) Security Forces Hospital, Riyadh; and (5) King Abdulaziz Medical City, Riyadh. All native kidney biopsies of the adult Saudi population performed in these centers from

January 1998 to December 2017 were included in this study. An adult was defined as 18 to 65 years old at the time of biopsy. If a patient had multiple biopsies with a glomerular disease diagnosis, only the first biopsy was retained for this study.

All renal biopsy specimens were processed by standard light, immunofluorescence, and electron microscopy procedures. Diagnoses were made by nephropathologists. Clinical, demographic and laboratory data, and renal histopathological diagnoses were collected from patient medical records. Indications for renal biopsy were: nephrotic syndrome or nephrotic range proteinuria, acute nephritic syndrome (ANS), rapidly progressive glomerulonephritis (RPGN) syndrome, chronic nephritic syndrome, asymptomatic hematuria with proteinuria, and acute kidney injury (AKI). The biopsy periods were categorized into four consecutive 5-year time intervals (1998-2002, 2003-2007, 2008-2012, and 2013-2017) for data analysis. Glomerular disease subtype frequency was our primary outcome. For the secondary outcomes, we also examined the clinical presentation and trends in glomerular disease frequencies within the demographic subgroups. The research was performed in compliance with the Declaration of Helsinki and was approved by the ethics committee of King Khalid University Hospital Institutional Review Board (E12-811). Informed consent was not required.

All the data were analyzed by SAS version 9.1. Continuous variables in the descriptive analysis were reported as mean and standard deviation or median, whichever was appropriate, while categorical variables were expressed as frequencies. When comparing different eras, *P* values for the trend were reported. We used the chi-square test and Fisher's exact test for categorical variables, and the one-way analysis of variance for continuous variables. A *P* value of <.05 was considered statistically significant.

## RESULTS

During the four biopsy eras (1998-2002, 2003-2007, 2008-2011, and 2012-2017), 1760 native renal biopsies were performed. Non-Saudis (231 cases), cases younger than 18 years old (326 cases) or older than 65 years old (74 case) and those with incomplete records (59 cases) were excluded, leaving 1070 cases enrolled in this study (**Table 1**). There were 579 (54.1 %) women and the mean age at biopsy was 36 years old. One fourth of the patients had a history of systemic lupus erythematosus (SLE) and almost one fifth had diabetes. The mean serum creatinine was 190  $\mu\text{mol/L}$ ; 48.5% of the patients had abnormal serum creatinine (above

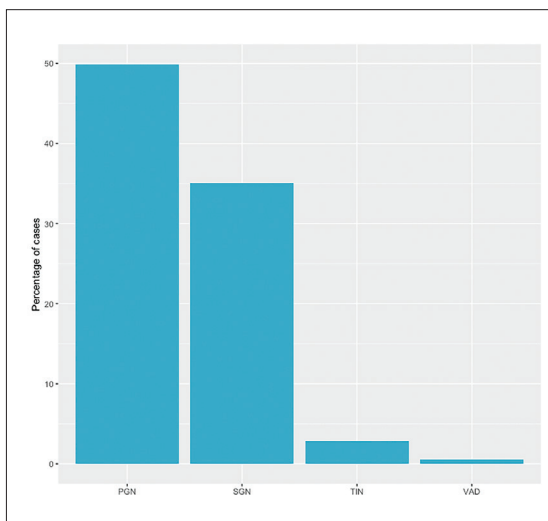
**Table 1.** Demographic and clinical characteristics of 1070 adults who underwent kidney biopsy from 1998 to 2017 in five major medical centers in Saudi Arabia.

Age at biopsy (mean, SD)	36.3 (12.3)
<b>Sex</b>	
Male	491 (45.9)
Female	579 (54.1)
<b>Clinical presentation</b>	
<i>Incidental finding</i>	
Asymptomatic hematuria	12 (1.1)
Asymptomatic proteinuria	95 (8.9)
Asymptomatic hematuria/ proteinuria	37 (3.5)
Nephritic syndrome	86 (8.0)
Nephrotic syndrome	426 (39.8)
Gross hematuria	100 (9.3)
Abnormal renal function	519 (48.5)
Elevated blood pressure	601 (56.2)
<b>Comorbidities</b>	
Diabetes mellitus	192 (17.9)
Malignancy	17 (1.6)
Hepatitis C infection	19 (1.8)
Hepatitis B infection	16 (1.5)
Systemic lupus erythematosus	271 (25.3)
<b>Laboratory results</b>	
Urine protein	4.1 (9.5)
Median	2.5
Serum albumin	28.6 (9.1)
Serum creatinine	190 (198)
Median (IQR)	120 (72-216)

Data are number (percentage).

120  $\mu$ mol/L) and 78 patients (7.3%) were on dialysis at time of biopsy. There was marked increase in the number of kidney biopsies performed in the most recent era. Approximately, half of the patients had a primary glomerular disease (**Figure 1**) and only 2.8% had tubulointerstitial disease.

The most frequent indication for renal biopsy was nephrotic syndrome in those with FSGS, minimal change disease (MCD), and membranous nephropathy (MEM), whereas renal impairment was the main indication for those with IgA nephropathy and MPGN. The

**Figure 1.** The distribution of histological diagnosis as determined by the kidney biopsies in 1070 Saudi adults from 1998 to 2017. The frequencies of the main groups are shown as a proportion of the whole cohort. PGN: Primary glomerular disease; SGN: Secondary glomerular disease; TIN: Tubulointerstitial disease; VAD: vascular disease.

other indications for kidney biopsies were stratified according to the glomerular diseases and are shown in **Table 2**. Overall, FSGS was the most common primary glomerulonephritis (GN) diagnosed histologically, accounting for 39.8% of the cases (**Table 3**). Sex and age distributions by glomerular disease subtypes are shown in **Table 3**. Renal biopsy frequencies by study period era and glomerular disease subtype are provided in **Figure 2**.

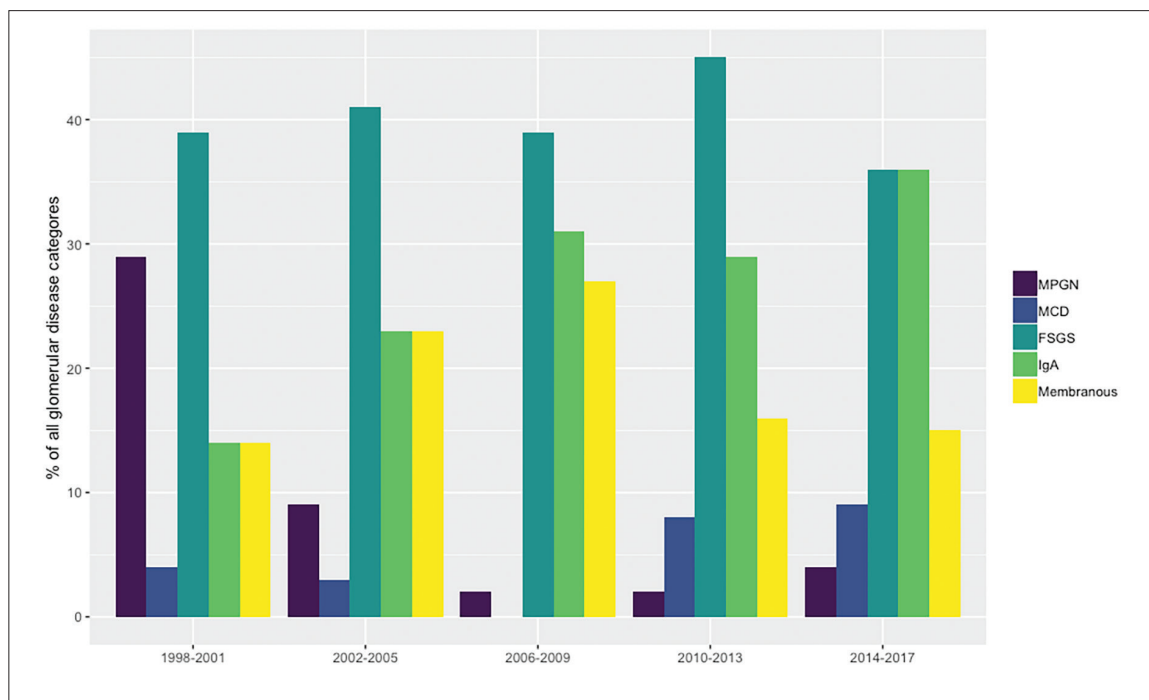
IgA nephropathy was the second most frequent GN diagnosis (29.2%), followed by membranous nephropathy (17%), minimal change nephropathy (6.9%), and MPGN (7.1%). IgA nephropathy was more predominant in men for primary GN ( $P < .001$ ). Minimal change disease remained unchanged over the last two decades (**Table 4**, **Figure 2**). However, MPGN has devolved significantly, from being the second most common primary glomerular disease to be the least reported type of primary GN in the most recent era. Currently, IgA has increased progressively from being the second least frequent glomerular disease to being almost as frequent as FSGS, the most common primary GN. Membranous nephropathy decreased significantly over the last era.

Lupus nephritis secondary to systemic lupus erythematosus (SLE) had the highest prevalence among the reported secondary GN types at 24.8%. Diabetic nephropathy had the second highest prevalence noted at 6.7% (**Table 5**). Anti-neutrophil cytoplasmic antibodies

**Table 2.** Indications for kidney biopsy of primary glomerular disease diagnoses among 1070 adults in Saudi Arabia from 1998 to 2017.

Indications for kidney biopsy	Histological pattern				
	FSGS	MPGN	MCD	MEM	IgAN
Nephrotic syndrome	97 (45.5)	7 (18.4)	24 (70.6)	69 (75.8)	38 (24.5)
Unexplained renal impairment	49 (23)	17 (44.7)	2 (5.9)	9 (9.9)	85 (54.8)
Asymptomatic urinary abnormalities	37 (17.4)	2 (5.3)	5 (14.7)	7 (7.7)	11 (7.1)
Nephritic syndrome	11 (5.2)	8 (21.1)	2 (5.9)	0 (0)	21 (13.5)
Non-nephrotic proteinuria	19 (8.9)	4 (10.5)	1 (2.9)	6 (6.6)	0 (0)
<b>Total</b>	213	38	34	91	155

Data are number (percentage). Frequencies of the different subtypes shown as a proportion of the primary glomerular disease cohort. FSGS: focal segmental glomerulosclerosis, MPGN: membranoproliferative glomerulonephritis, MCD: minimal change disease, MEM: membranous nephropathy, IgAN, Immunoglobulin A nephropathy;



**Figure 2.** Temporal trends in the relative renal biopsy frequencies of primary glomerular disease subtypes, 1998-2017. Frequencies of the different subtypes shows as proportion of the primary, glomerular disease cohort. , MPGN: membranoproliferative glomerulonephritis, MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; IgAN: Immunoglobulin A nephropathy.

(ANCA), pauci-immune GN, and Alport syndrome were among the more rare subtypes with biopsy frequencies of 2% or less. It was not feasible to do temporal trends because of the small number of cases. The frequency of diabetic nephropathy in renal biopsy specimens increased dramatically over the last two decades, from 1.4% in the first era to 10.2% in the last era (*P* value for the trend .001; **Table 6**).

## DISCUSSION

This review of kidney biopsies demonstrated more primary GN than secondary GN in our studied population. FSGS was the most common primary GN in the pathology reports. This is expected, given the high incidence of FSGS compared to other glomerular diseases globally. There are a lack of data on the prevalence of genetic variants associated with FSGS (e.g. APOL1 gene)

**Table 3.** Sex and age characteristics for the primary glomerular diseases (n=535).

Primary GN Subtypes	n (%)	Mean age (y)	M:F ratio	P value for comparison of sexes <sup>a</sup>
FSGS	213 (39.8)	38.3	1.2 :1	<b>.01</b>
MCD	37 (6.9)	30.4	1.5 :1	.1
MEM	91 (17)	37.0	1.3 :1	<b>.05</b>
IgAN	156 (29.2)	36.4	2 :1	<b>.001</b>
MPGN	38 (7.1)	33.9	0.9 :1	.9

GN: glomerulonephritis, FSGS: focal segmental glomerulosclerosis, MCD: minimal change disease, MEM: membranous nephropathy, IgAN, immunoglobulin A nephropathy, MPGN: membranoproliferative glomerulonephritis. <sup>a</sup>Chi-squared test

**Table 4.** Temporal trends in renal biopsy frequencies of all primary glomerular disease subtypes.

Glomerular disease	1998-2002 n=148	2003-2007 n=96	2008-2012 n=253	2013-2017 n=572	P value for trend <sup>a</sup>
FSGS	35 (23.6)	19 (19.8)	61 (24.1)	98 (17.1)	.07
MCD	3 (2.0)	1 (1.0)	10 (4.0)	22 (3.8)	.4
MEM	15 (10.1)	9 (9.4)	32 (12.6)	35 (6.1)	<b>.01</b>
IgAN	11 (7.4)	12 (12.5)	36 (14.2)	97 (17)	<b>.03</b>
MPGN	22 (14.9)	3 (3.1)	4 (1.6)	9 (1.6)	<b>.001</b>

Data are number (percentage). GN: glomerulonephritis, FSGS: focal segmental glomerulosclerosis, MCD: minimal change disease, MEM: membranous nephropathy, IgAN, immunoglobulin A nephropathy, MPGN: membranoproliferative glomerulonephritis. <sup>a</sup>Chi-squared test

**Table 5.** The common secondary glomerular disease diagnoses among the 1070 adults who underwent kidney biopsy in Saudi Arabia from 1998 to 2017.

Systemic lupus erythematosus	266 (24.8)
Diabetic nephropathy	72 (6.7)
Acute interstitial nephritis	15 (1.4)
Hypertensive nephrosclerosis	7 (0.6)
ANCA-associated	15 (1.4)
Amyloidosis	7 (0.6)
Anti-GBM	9 (0.8)
Alport syndrome	6 (0.5)

Data are number (percentage). ANCA: anti-neutrophil cytoplasmic antibodies, Anti-GBM: anti-glomerular basement membrane. The frequencies of the different subtypes are shown as a proportion of the kidney biopsy cohort.

among Saudis.<sup>16</sup> The prevalence of obesity, which is a known cause of secondary FSGS,<sup>17</sup> has been increasing among Saudis to 28.7%<sup>18</sup> and that may explain the increased incidence of this glomerular subtype. We found significant changes in the incidences of primary glomerular diseases over the past two decades. Like the trends of MPGN in the United States and in Asia,<sup>19,7</sup> the incidence of this glomerular disease has been declining in Saudi Arabia. Further classification of the MPGN subtypes and patterns (Type I versus Type III; immune complex mediated versus complement induced) may help in determining the cause of these changes.

There has been an increased reporting of IgA nephropathy in recent years compared to earlier times. This increase has been reported from registries in China, the United States, and Europe.<sup>7,19-21</sup> In the past

**Table 6.** Temporal trends in renal biopsy frequencies of common secondary glomerular disease subtypes.

	1998-2002 n=148	2003-2007 n=96	2008-2012 n=253	2013-2017 n=572	P value for the trend <sup>a</sup>
Systemic lupus erythematosus	44 (29.7)	31 (32.2)	68 (26.9)	123 (21.4)	<b>.03</b>
Diabetic nephropathy	1 (1.4)	3 (3.1)	10 (3.9)	59 (10.2)	<b>.001</b>

Data are number (percentage). <sup>a</sup>Chi-squared test

five years, reports of IgA nephropathy have matched that of FSGS. To our knowledge, there are no demographic or genetic changes to account for this phenomenon. Based on recent studies, a possible cause for the increased reporting of IgA nephropathy may be the dietary and environmental changes affecting gut microbiota.<sup>22</sup> The recent increased consumption of fast food among the Saudis may influence gut microbiota profiles.<sup>23</sup>

Among the secondary GN, lupus nephritis was the most common reported pathology. We expected a higher number of diabetic nephropathy cases reported among the study patients (6.7%), given the presence of diabetes as a co-morbidity in 17% of the study population and the high prevalence of diabetes mellitus in Saudi Arabia.<sup>24</sup> Such results may also be related to clinical practice, wherein only a few diabetic patients undergo kidney biopsy.

In this study, we measured laboratory parameters such as serum creatinine and quantified urine protein, which can help in determining the severity of the reported glomerular diseases. Many patients already had renal impairment at the time of biopsy, presenting with severe or advanced (and possibly late presenting) kidney diseases. We suspect that this was due to the aggressive state of the diseases. There is a high incidence of reported FSGS and IgA nephropathy among the study patients, and they are both known to present with renal impairment. Though the biopsies were performed in five major tertiary hospitals and reviewed by qualified nephrologists, these hospitals received

referrals from other provinces in Saudi Arabia and that has limited our ability in determining regional geographic variability in the trends of different glomerular diseases. Another potential limitation is the retrospective design of this study; data was gathered based on the information at the time of biopsy. Potential secondary diagnosis may not have been available at the time of biopsy. However, the effect of this is likely limited by the routine screening tests (such as hepatitis B virus screening and antinuclear antibodies required in all hospitals prior to requesting a kidney biopsy).

We have chosen to exclude kidney biopsies of patients older than 65 years of age because the incidence of some glomerular diseases can be higher in this age group. Specifically, membranous nephropathy and pauci-immune GN seem to be the dominant primary and secondary glomerular diseases in this age group, respectively.<sup>25</sup> A specified analysis of patients in this age group may help yield some important information that may have been missed if this group was analyzed with other adults.

With the changes in the reporting of the trends of different glomerular diseases over the past two decades among Saudi patients, future studies should focus on potential genetic and environmental factors that may account for these. Specifically, the rise of IgA nephropathy over the past five years is alarming. Though they may be difficult to perform, the use of screening programs to determine the true prevalence of IgA nephropathy in Saudi Arabia may help in understanding the true burden of this disease.

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