

Glomerulonephritis disease pattern at Saudi tertiary care center

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ABSTRACT

الأهداف: لتقييم التغيرات في نمط الأمراض الكبيبي للمساعدة في توجيه التخصيص الأمثل للموارد، والتركيز على البحث في المستقبل، وتحسين النتائج.

الطريقة: أجريت مراجعة بأثر رجعي على خزعات الكلى التي أجريت خلال الفترة من 2007م و 2016م في مركز رعاية صحية واحد في المملكة العربية السعودية (مدينة الملك فهد الطبية، الرياض) لتقييم انتشار ونمط التهاب كبيبات الكلى (GN).

النتائج: كان GN الابتدائي الأكثر شيوعاً في 102 خزعة من المرضى البالغين الذين تتراوح أعمارهم بين 13.6±28.9 سنة و 40.2% من الإناث، كبيبي والتصلب الكبيبي القطعي (35.3%). ومن بين 64 مريضاً مصاباً بالتهاب الكلية الذئبي الحامى المرتبط به، وكان معظمهم (82.8%) من الإناث، وكان التهاب الكلية الذئبي (46.9%) 4 (LN)، و 3 (LN) (32.8%) من الطبقات الأكثر شيوعاً لالتهاب الكلية الذئبي.

الخاتمة: إنشاء سجلات GN المحتملة التي يمكن الحصول عليها من بيانات التشخيص والعلاج والنتائج القوية أمر ضروري؛ غير أن تطوير السجلات وصيانتها كثيراً ما يحول دون تقييد الموارد. وبناء على ذلك، سيستمر تحليل البيانات الإدارية بأثر رجعي في توفير معلومات تكميلية هامة عن علم الأوبئة في GN.

Objective: To assess changes in the pattern of glomerular diseases to help guide optimal allocation of resources, to focus future research, and improve outcomes.

Methods: A retrospective chart review was conducted on kidney biopsies taken between 2007 and 2016 at a single tertiary care center in Saudi Arabia (King Fahad Medical City, Riyadh) to evaluate the prevalence and pattern of glomerulonephritis (GN).

Results: The most common primary GN in 102 biopsies from adult patients with a mean age of 28.9 ±

13.6 years and 40.2% female, was focal and segmental glomerulosclerosis (35.3%). Among 64 patients with systemic lupus erythematosus associated nephritis, of whom most (82.8%) were female, lupus nephritis (LN) 4 (46.9%), and (LN) 3 (32.8%) were the most common lupus nephritis classes.

Conclusion: Establishing prospective GN registries from which robust diagnosis, treatment, and outcomes data can be acquired is warranted; however, registry development and maintenance are often precluded by resource limitations. Accordingly, retrospective analysis of administrative data will continue to provide important complementary information on GN epidemiology.

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Glomerulonephritis (GN) is an inflammation of the capillaries of the glomeruli, characterized by albuminuria, edema, and hypertension. Serious complications of GN include acute renal failure and end stage renal disease (ESRD). Glomerulonephritis is the third leading cause of ESRD in the United States after diabetes and hypertension.¹ In the Kingdom of Saudi Arabia, GN is the third leading cause of ESRD after diabetes, estimated to be responsible for 3.7% of

cases.² Longitudinally reviewing changes in the pattern of glomerular disease prevalence can facilitate designing appropriately focused research on the etiology, pathology, and management strategies across GN types. After a report was published in 2000 describing a series of 782 biopsies acquired at 6 referral hospitals in the Kingdom during an undefined time interval,³ a paucity of additional reports became available on the spectrum of GN in the Kingdom. A retrospective analysis of 296 biopsy samples acquired between 1989 to 2007 from adults in the Western region of Saudi Arabia was performed,⁴ and data from single centers in Riyadh representing 120 biopsies performed from 1990 to 2001⁵ and 348 biopsies performed from 2005 through 2009 were reported.⁶ To supplement these reports with more recent data, a retrospective review was performed on 166 kidney biopsies performed from 2007 to 2016 at King Fahad Medical City (KFMC), Riyadh, which is a referral center for patients representing all regions of the Kingdom of Saudi Arabia (KSA).

Methods. Native kidney biopsies were obtained from 183 patients at KFMC, Riyadh, KSA, between 2007 and 2016. Biopsies with complete data available, which were obtained from patients with primary GN or with systemic lupus erythematosus (SLE)-associated secondary GN, were included in this review. Additional eligibility included age ≥ 12 years, which is defined as adult by local authorities. Patients were referred from hospitals throughout the Kingdom or from within KFMC, including the emergency room. Indications for kidney biopsy were proteinuria (nephrotic range or, with SLE >500 mg/day), renal insufficiency, or hematuria.

Biopsies were performed by interventional radiologists under ultrasound guidance, using Tru-Cut biopsy needles. Two to 3 cores of renal tissue were obtained. Sample adequacy was defined as the presence of at least 10 glomeruli, which was confirmed on-site by a pathology lab technician. Samples were processed at KFMC and at the National Guard Hospital, Riyadh, by a nephro pathologist using light microscopy, immunofluorescence, and electron microscopy. Institutional review board approval was obtained before the data were collected.

Data were summarized and means and standard deviations calculated. The Chi-Square and Fisher Exact tests were used to compare proportions, with $p < 0.05$ indicating a significant difference between groups.

Results. Of 166 qualifying native kidney biopsies, 102 (61.4%) had primary GN and 64 (38.6%) had SLE-associated GN. In the primary GN cohort, 59.8% of patients were male and 40.2% were female,

and were an average of 28.9 ± 13.6 years at the time of the biopsy (range, 13-70 years). The most common primary glomerular diseases were focal segmental glomerulosclerosis (FSGS; 35.3%), minimal change disease (MCD; 26.5%), and membranous nephropathy (MGN; 12.7%) (Table 1). Female prevalence was 47.2% in FSGS, 29.6% in MCD, and 38.5% in MGN.

Among 64 patients with SLE-associated GN, 17.2% were male and 82.8% were female, with an average age of 26 ± 10.7 years at the time of the biopsy (range, 14-60 years). Significantly more SLE GN patients were female compared with the primary GN group (82.8% versus 40.2%, $p < 0.0001$). Lupus nephritis (LN) types were primarily LN4 (46.9%) and LN3 (32.5%) (Table 2).

Thirty-one of our patients (18.7%) were between 13 and 17 years of age. Excluding these patients, proportions of disease types were slightly different in the resulting subgroup of patients who were ≥ 18 years of age compared with the type proportions in the entire cohort; however, rank order of type prevalence did not vary between groups (data not shown). For example, among 83 primary GN patients aged ≥ 18 years, MCD was observed in 21 (25.3%) biopsies, compared with 6 of 19 (31.6%) biopsies of patients aged 13 through 17 years ($p = 0.79$), and 27 (26.5%) biopsies in the entire primary GN cohort of 102 biopsies ($p = 0.86$). Membranous nephropathy was responsible for 12 (14.5%) of GN cases in patients ≥ 18 years, compared with 1 (5.3%) patient aged 13 through 17 ($p = 0.45$), and 13 (12.7%) patients in the entire primary GN cohort ($p = 0.74$).

Discussion. The prevalence of GN disease states has been shown to vary with time and location worldwide, and the Kingdom is no exception. Several small studies have been reported from the Kingdom with divergent observations. Focal segmental glomerulosclerosis is typically reported as the most common primary GN; however, MCD, MGN, and MPGN have also been reported to have the highest prevalence, although longitudinal data from similar catchment areas are not available.⁶ Registry data were published in 2000 from 4 hospitals in Riyadh, one in Jeddah, and one in the eastern province, which included 782 adult patients with GN.³ Similar to our patients, FSGS was also the predominate pattern, observed in 21.3% of adult biopsies with primary GN. However, it was more prevalent in our patients (35.3%) compared with that earlier study. A U.S. managed care study reported 38.9% of 2,501 GN patients ≥ 18 years of age had FSGS, which increased from a rate of 1.6 per 100,000 person-years in 2000 to

Table 1 - Primary Glomerulonephritis in 102 Patients: 2007-2016.

Variable	Male		Female		Total	
	n	(%)	n	(%)	n	(%)
Total	61	(59.8)	41	(40.2)	102	(100.00)
Minimal change disease	19	(69.4)	8	(29.6)	27	(26.5)
Membranous glomerulonephritis	8	(61.5)	5	(38.5)	13	(12.7)
Focal segmental glomerulosclerosis	19	(52.8)	17	(47.2)	36	(35.3)
Membranoproliferative glomerulonephritis	3	(50.0)	3	(50.0)	6	(5.9)
Immunoglobulin A nephropathy	7	(87.5)	1	(12.5)	8	(7.8)
Granulomatosis with polyangiitis	2	(50.0)	2	(50.0)	4	(3.9)
Anti-glomerular basement membrane disease	0	-	1	(100.0)	1	(1.0)
Post-Infectious glomerulonephritis	2	(50.0)	2	(50.0)	4	(3.9)
C1q Disease	0	-	1	(100.0)	1	(1.0)
Thrombotic thrombocytopenic purpura	1	(50.5)	1	(50.0)	2	(2.0)

FSGS - focal segmental glomerulosclerosis, IgAN - immunoglobulin A nephropathy, GBMD - glomerular basement membrane disease, GPA -granulomatosis with polyangiitis, MCD - minimal change disease, MGN - membranous glomerulonephritis, MPGN - membranoproliferative glomerulonephritis, PIGN - post-infectious glomerulonephritis, TTP - thrombotic thrombocytopenic purpura

Table 2 - Systemic lupus erythematosus-associated glomerulonephritis in 64 patients: 2007-2016.

Variable	Male		Female		Total	
	n	(%)	n	(%)	n	(%)
Total	11	(17.2)	53	(82.8)	64	(100.0)
Lupus nephritis class 2	2	(18.2)	9	(81.8)	11	(17.2)
Lupus nephritis class 3	4	(19.0)	17	(81.0)	21	(32.8)
Lupus nephritis class 4	5	(12.7)	25	(83.3)	30	(46.9)
Lupus nephritis class 5	-	-	2	(100.0)	2	(3.1)

5.3 cases in 2011.⁷ The overall increased GN rates in the 12-year observation interval in the U.S. study were driven by increases in FSGS and also in IgA nephropathy (IgAN), which underwent a 16-fold rate increase from 0.1 in 2000 to 1.6 in 2011 (per 100,000 person years). However, IgAN was only slightly higher in our cohort compared with its prevalence in the earlier KSA registry data (7.8% versus 6.5%).³ In a study in Western KSA, IgAN was the third most common primary GN, present in 17.6% of biopsies acquired from 296 adults during the 18-year interval from 1989-2007.⁴ Minimal change disease was represented in 25.3% of our primary cases

≥18 years of age, which is considerably more than the 11.6% prevalence reported for the sample included in the KSA registry study published in 2000.³ Patients in that study were 30.8 ± 15.1 years of age, which is similar to the 28.9 ± 13.6 years in our study. Minimal change disease was also considerably less prevalent (11%) in older patients (50.6 ± 16.7) comprising the U.S. healthcare system sample of patients aged ≥18 years.⁷

Membranous nephropathy was more common in our sample (14.5% in patients ≥18 years) compared with that in the registry data from 2000 (10.6%).³ In the Western KSA study, MGN was the most common GN type, noted in 25.7% of the biopsies.⁴ In the U.S. data, the MGN case rate increased from 0.7 to 1.4 (per 100,000 person years) between 2000 and 2011.⁷

Membranoproliferative glomerulonephritis and MsPGN were identified in biopsies from 20.7% and 16.3% of patients in the 2000 KSA registry study;³ while MPGN was present in 5.9% of our patients. Membranoproliferative glomerulonephritis may be less prevalent in our cohort in response to improved control of infections, including hepatitis C virus.

The 1% C1q nephropathy prevalence in our sample, represented by a single patient, is less than the 0.2% to 2.5% commonly observed in biopsies from children and adults.⁸ Although C1q nephropathy was proposed as a distinct clinical entity over 30 years ago, its status remains controversial and it continues to be poorly

understood.⁹ In fact, several reports include FSGS and MCD as subtypes within C1q nephropathy cohorts.

Renal involvement is common in SLE. In a study of 47 women with SLE throughout the Kingdom, renal involvement characterized by proteinuria, hematuria, or nephrotic syndrome was observed in 57.4% of patients.¹⁰ In addition, confirmed GN was reported in 27 of 46 patients (58.7%) from Eastern Saudi Arabia,¹¹ and in 299 of 624 (47.9%) patients diagnosed with SLE from 1980 to 2006 in a tertiary care referral hospital in Riyadh.¹² Likewise, most studies in the Kingdom have reported LN as the most common cause of secondary GN.⁶ The 38.6% prevalence of LN in our entire cohort was much higher than that reported in other series. In the largest study from the Kingdom, reported in 2000, SLE was associated with 126 GN cases; 17.7% of the cohort comprised primary and LN cases.³ In most studies from the Kingdom, LN4 predominates among SLE patients with GN.¹³ Almost half (46.9%) of our SLE patients had LN4, compared with 37.1% LN4 prevalence in a cohort of 299 SLE patients with GN reported from a hospital in Riyadh.^{12,14} In that study, only 10% had LN3 compared with 32.8% of our patients, while 14.4% had \geq LN5, compared with 3.1% of our SLE patients. Although LN class was not associated with survival in that study, LN3 ($p=0.013$) and LN4 ($p=0.039$) were significant risk factors for progression to ESRD.

Determining the pattern of GN is an important aspect of early detection, and epidemiologic study data can promote cost effective screening, and allow focused research efforts on preventing GN and improving patient care across the specific GN forms. Within glomerular diseases, such as LN and IgAN, further classifications using morphologic data have been proposed, in attempts to enhance the ability to provide prognostic information within a diagnosis.¹⁵ However, the lack of standardization and universal validation of methods for classifying and reporting GN continue to plague these efforts. Several systems have been implemented or proposed, which often are not comprehensive in scope. A consensus meeting endorsed by the Renal Pathology Society was held in 2015, which promoted a pathogenesis-based classification of GN, with guidelines for standardized GN reporting.¹⁶ However, MGN, MCD, and FSGS were among the glomerular diseases that were not included in the classification system. Data from South Asia and the Middle East are notably lacking in studies of general and specific classifications,¹⁷ with a single report from Iran exploring the Oxford-MEST IgAN classification in 102 IgAN patients.¹⁸

In conclusion, our data contribute to documenting and understanding the epidemiology of GN in the Kingdom; however, our study has the inherent weaknesses associated with retrospective studies. Further studies are warranted, with more detailed analysis of disease characteristics, interventions, disease progression and outcomes, and potential prognostic variables. Although there are numerous benefits of a GN registry designed to acquire data prospectively, establishing comprehensive registries is often precluded by resource limitations. Accordingly, retrospective analyses of administrative data, such as that included in this report, can provide an important complementary approach to studying GN epidemiology.¹⁹

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