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A Study of the Clinico-Histologic Patterns of Adult Glomerulonephritides in South western Nigeria

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ABSTRACT

Background: Glomerulonephritis (GN) is one of the major causes of chronic kidney disease (CKD) worldwide. It remains the leading cause of End Stage Kidney Disease (ESRD) in many developing countries. It is presumed to be responsible for more than half of patients with ESRD in Africa. The clinical course, pattern and presentation of glomerular disease varies world-wide and may be due to differences in genetics of underlying population or exposure to putative antigens or agents that induce or trigger these responses. This study evaluated the clinicopathologic patterns of glomerular diseases in a homogenous black population in the hope that it will provide a more robust data on glomerulonephritides in our black population. The study is aimed at describing the pattern of biochemical abnormalities and histopathologic variants of glomerulonephritides observed in adult patients in our environment.

Methods: The study was cross-sectional inature involving seventy (70) consecutive adult patients with features of glomerulonephritis who presented at the nephrology and other medical out-patient department (MOPD) clinics, general out-patient department (GOPD) as well as the hospital staff clinic. A structured 4-part proforma was drawn up and administered to obtain information on socio-demographic, clinical, anthropometric parameters and laboratory investigation results. Relevant laboratory tests and investigations were performed. Renal function was assessed and renal biopsy performed after obtaining written informed consent. The renal tissues obtained were subjected to light microscopy and immunoperoxidase staining with IgA, IgM, IgG and C_3 antibodies and the results interpreted.

Results: A total of seventy patients participated and completed the study. Three (3) patients had inadequate renal tissue for histologic diagnosis hence data analysis was based on the remaining sixty seven (67) patients.The age range of the study population was between 18 and 65 years with a mean age of 28.43 (±10.33) years. Forty- five males (67.2%) and twenty-two females (32.8%) participated in the study population with an overall male to female ratio of 2:1. The most common clinical manifestation was nephrotic syndrome which was present in 41 (61.2%) of the study population. The most common histological diagnosis was focal segmental glomerulosclerosis (FSGS) seen in 30 patients (44.8%).

Conclusion: Focal segmental glomerulosclerosis (FSGS) was the commonest histological type found in these patients with glomerulonephritis, while the commonest clinical presentation was nephrotic syndrome.

Keywords: *Glomerulonephritides, histologic diagnosis, nephrotic syndrome, renal biopsy, focal segmental glomerulosclerosis.*

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INTRODUCTION

Glomerulonephritis (GN) is one of the major causes of chronic kidney disease (CKD) worldwide.[1]It remains the leading cause of End Stage Kidney Disease (ESRD) in many developing countries including Nigeria.[1,2,3]It is presumed to be responsible for more than half of patients with ESRD in Africa.[4] The clinical course, pattern and presentation of glomerular disease varies world-wide and may be due to differences in genetics of underlying population or exposure to putative antigens or agents that induce or trigger these responses.[5]Glomerulonephritis has been shown to be commoner in the younger age group and this may account for the higher incidence of CKD and ESRD among young people in the Sub-Saharan Africa (SSA) compared to the developed countries where it mostly affects middle aged and older individuals.[1,2,3]

Renal biopsy is an important diagnostic tool in the clinical evaluation and treatment of many cases of chronic kidney disease of which glomerulonephritis account for a significant percentage. Data from Africa relating to biopsy proven glomerulonephritis are few and most are single centre and hospital-based studies. Most of the studies done in this environment have been based on clinical presentation and not kidney biopsy or histological evidence of GN.[2,3] Limited studies that had kidney biopsy done had reports on light microscopy and very rarely immunoperoxidase.[6,7] Only a few study had light microscopy, immunofluorescence and electron microscopy done on the renal biopsy tissue.[8] This cross sectional study was conducted to evaluate the clinicopathologic patterns of glomerular diseases in a homogenous black population using a tertiary hospital in Osun State. This study in contrast to some of the studies that had been done in the past has reports of both light microscopy and immunohistochemistry.

MATERIALS AND METHODS

This cross sectional study involved Seventy (70) consecutive adult patients aged between eighteen (18) and sixty-five (65) years with clinical features of glomerulonephritis who fulfilled the inclusion criteria at the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC) Ile-Ife. Ethical approval was obtained from the hospital ethics committee and the patients recruited after obtaining written informed consent. The inclusion criteria included:

1. All consenting patients between ages 18 and 65 years with the diagnosis of glomerulonephritis as defined by;

- Past history of body swelling.
- Past history of acute or post infectious glomerulonephritis (PIGN).
- Passage of dark coloured urine.
- Hypertension.
- Haematuria, dysmorphic red cell cast/ granular cast in the urine.
- Detectable proteinuria $\geq$ 500mg/day.

2. Patients with asymptomatic proteinuria and/or haematuria. While exclusion criteria were:

- Known causes of proteinuria such as fever, exercise, congestive cardiac failure (CCF), Bence Jones proteinuria, multiple myeloma and haemoglobinuria.[9,10]
- Individuals diagnosed with glomerulonephritis who are on immunosuppressive therapy
- Active urinary tract infection on urine microscopy.[9,10]
- Pregnancy.[9,10]
- Small kidneys (bipolar diameter less than 9cm on ultrasound).[9,10]
- Solitary kidney[9,10]
- Obstructive uropathy.[9,10]
- Uncontrolled severe hypertension (BP>160/ 95mmHg).[9,10]
- Bleeding diathesis (bleeding time >10mins,PT/ APTT >1.2 times control).[9,10]
- Thrombocytopaenia (Platelet count < $100x10^9/L$).[9,10]
- Anaemia (Hb< 10g/dl).[9,10]
- Known causes of red coloured urine such as haemoglobinuria, myoglobinuria or porphyrias.[9,10]

A structured four part proforma was drawn up and administered to obtain clinical information and

laboratory investigation results. Relevant laboratory tests and investigations were performed prior to kidney biopsy.The following were the indications for renal biopsy in the patients who presented with clinical features suggestive of glomerulonephritis

(1) Nephrotic range proteinuria defined as urinary protein excretion > 3.5gm in 24 hours.[9,10]
(2) Nephritic syndrome defined as haematuria (red cell cast), hypertension (BP > 140/90mmHg), reduced eGFR and proteinuria < 3g/24hours and oedema all in < 3months .[9,10]
(3) Persistent asymptomatic proteinuria > 500mg/ 24hours for at least 3 months.[9,10]
(4) Persistent asymptomatic haematuria for at least 3 months with dysmorphic RBC on urine microscopy.[9,10]
(5) Nephritic-nephrotic syndrome defined as the presence of haematuria (red cell cast), hypertension (BP > 140/90mmHg), reduced eGFR and proteinuria > 3.5gm/day with or without oedema.[9,10]

Percutaneous renal biopsy was done using an automated spring-loaded biopsy needle (Bard Peripheral Vascular Inc 1625 West 3rd Street Tempe, A2 85281, USA 16 gauge size) under real time ultrasound guidance following standard procedure and strict asepsis. The renal tissue obtained was fixed in formalin and processed for light microscopy and immunoperoxidase staining using four panels of antibodies mainly IgA, IgM, IgG and C3 after antigen retrieval was done in the histopathology unit of OAUTHC Ile- Ife, Osun state.

Data obtained was analysed using statistical package and social sciences (SPSS) version 20. Continuous data are expressed as means and standard deviations for normally distributed data and median with interquartile range for skewed data. Categorical data are summarized using frequencies and percentages. Means were compared using the Student's t-test or Analysis of variance test (ANOVA) while categorical variables were compared using chi-square or Fishers exact tests. Post hoc analysis was carried out as appropriate. The relationship between kidney function and renal histopathological findings was determined using Spearman's correlation coefficient and regression analysis as appropriate. A p-value of < 0.05 was regarded as statistically significant.

RESULTS

A total of seventy patients participated and completed the study. Three (3) patients had inadequate renal tissue for histologic diagnosis hence data analysis was based on the remaining sixty seven (67) patients.The age range of the study population was between 18 and 65 years with a mean age of 28.43 (±10.33) years. Sixty- two patients (92.5%) were in the age range of 18-44 years while age group 45-65years accounted for 7.5% of the study population. Sex distribution of the participants revealed 45 males (67.2%) and 22 females (32.8%) with an overall male to female ratio of 2:1. The other clinical characteristics of the study population are depicted in table 1.

Table 1: Characteristics of the study population

Patients Characteristics	**n (%)**
Number of patients	67
Age (years)	
18-44	62(92.5)
45-65	05(7.5)
Gender	
Male	45(67.2)
Female	22(32.8)
Weight (Kg)	63.4 ± 3.60
Serum Creatinine (µmol/L)	121.3 ± 6.69
eGFR (ml/min/1.73m^2)	85.8 ± 38.7
Serum albumin (g/L)	21.8 ± 6.6
Serum protein (g/L)	53.2 ±10.8
Serum total cholesterol(mmol/L)	9.63 ± 3.87
24 hour Urinary protein excretion(g/day)	6.17 ± 4.51
Haemoglobin (g/dL)	11.6 ± 2.54

Passage of frothy urine and generalised body swelling were the most common presentation seen in 64 (95.5%) and 59 (86.8%) of the study population respectively. Haematuria and hypertension accounted for 11.9% (8) and 29.9% (20) respectively. Majority of the study population were in stage 1 chronic kidney disease (CKD). Eight (8) of the thirty-two patients in stage 1 had eGFR (>135ml/min/1.73m^2) in the hyperfiltration range as shown in figure 1.

The most common clinical syndrome resulting in renal biopsy was nephrotic syndrome which was present in 41 (61.20%) followed by nephritic-nephrotic syndrome accounting for 20.9% while nephritic syndrome and AUA accounted for 13.4% and 3.0% respectively. Macroscopic haematuria accounted for 1.5% of the indications for renal biopsy. All the clinical syndromes had male preponderance

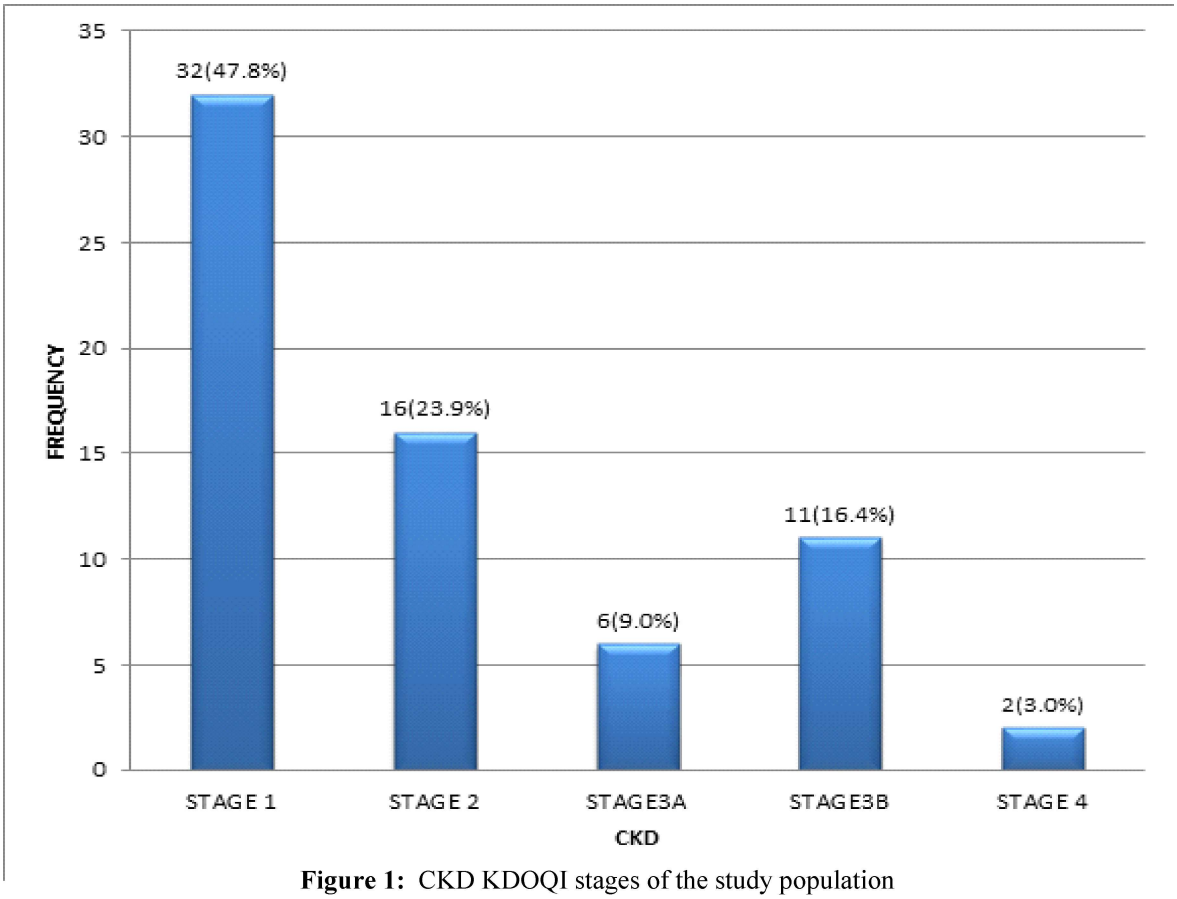

Figure 1: CKD KDOQI stages of the study population

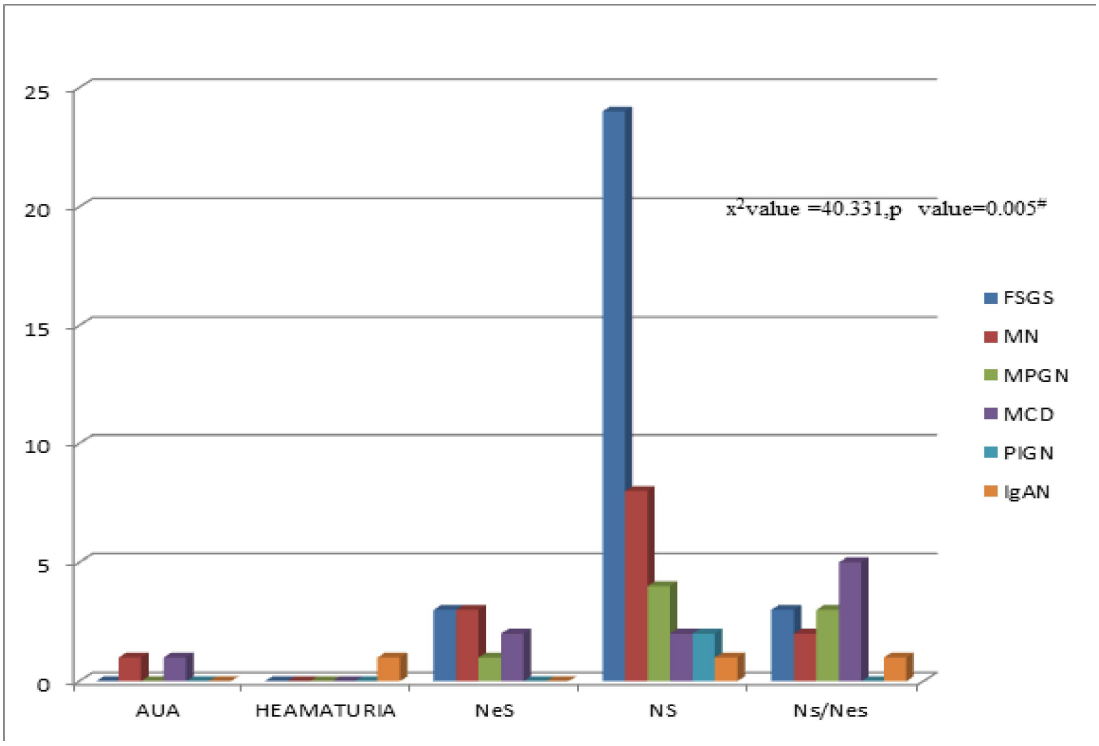

Figure 2: Distribution of histological diagnosis across clinical syndrome in the study population

FSGS- Focal segmental glomerulosclerosis, MN-Membranous nephropathy, MCD- Minimal change disease, PIGN Post infectious GN, MPGN Membranoproliferative GN, IgAN Immunoglobulin A Nephropathy, HAEM- Haematuria, CGN- Chronic glomerulonephritis; NS-Nephrotic syndrome; AUA- Asymptomatic urinary abnormality; NeS/NS-Nephritic-nephrotic syndrome; # Fisher exact test

except asymptomatic urinary abnormality which occurred only in females. The biochemical variations observed across the clinical syndromes with the p values is depicted in table 2.

Focal segmental glomerulosclerosis was the most common histological pattern present in 30 patients (44.8%). This is followed by membranous nephropathy MN seen in 14 (20.90%). Minimal change disease (MCD), membranoproliferative

Table 2: Laboratory parameters of the study population across clinical syndromes

Clinical syndrome	**Biochemical parameters, Mean (SD)**					
	Serum Albumin (g/L)	Serum Creatinine (µmol/l)	GFR (ml/min)	24hrs urinary protein (g/24hrs)	Cholesterol (mmol/l)	PCV (%)
HAEM	19.8(0.00)	58 (0.00)	160 (0.00)	2.80 (0.00)	9.60(0.00)	39.0(0.00)
AUA	22.5(3.50)	89.0(18.4)	80.9(16.30)	2.55(0.07)	4.45(3.18)	29.5(3.53)
Nephritic	31.2(6.40)	159.2(69.1)	63.4(39.10)	3.64(1.65)	6.81(3.02)	37.0(6.69)
Nephrotic	20.3(5.40)	114.1(45.1)	89.9(35.20)	8.53(1.44)	10.3(4.62)	35.2(7.28)
NeS/NS	20.4(5.76)	127.3(64.5)	83.5(44.9)	5.46(3.94)	10.1(2.96)	32.8(9.20)
F value	7.654	2.752	1.917	1.934	2.770	0.830
p value	**<0.001***	**0.026***	**0.028***	0.418	**0.035***	0.511

Table 3: Biochemical parameters across histological diagnosis in the styudy population

Histological pattern	**Biochemical Parameters, Mean (SD)**					
	Serum Albumin (g/L)	Serum Creatinine (µmol/l)	Cholesterol (mmol/l)	LDL (mmol/l)	24hr urinary protein (g/24hrs)	PCV (%)
MCD	23.6(8.32)	104.7(40.3)	9.32(3.62)	6.83(3.9)	5.91(4.49)	34.2(10.6)
FSGS	18.3(3.21)	133.0(60.7)	10.2(4.21)	7.60(4.19)	6.88(4.18)	33.5(7.21)
MN	23.0(8.19)	116.4(54.0)	8.80(4.09)	6.7I(3.87)	5.81(1.42)	37.2(6.77)
MPGN	21.8(5.70)	119.7(60.5)	9.64(3.55)	7.31(3.28)	5.71(2.08)	35.6(8.56)
PIGN	22.0(2.82)	104.0(82.7)	8.10(0.42)	5.25(1.77)	5.05(1.20)	40.5(0.71)
IgAN	21.1(5.88)	99.0(35.1)	10.4(3.82)	9.53(1.21)	3.60(0.72)	34.3(4.04)
F value	0.463	0.603	0.319	0.440	0.390	0.469
p value	0.802	0.698	0.900	0.819	0.854	0.889

Table 4: Relationship between urinalysis findings and histological diagnosis

Histologic diagnosis	Proteinuria N (%)	Proteinuria & haematuria N (%)	df	x^2	P value
MCD					
Yes	7 (70.0)	3(30.0)	1	6.635	**0.010*#**
No	52(91.2)	5(8.8)			
FSGS					
Yes	28(93.3)	2(6.7)	1	1.437	0.231
No	31(8e3.8)	6(10.2)			
MPGN					
Yes	6(75.1)	2(25.0)	1	1.474	0.225
No	53(89.9)	6(10.2)			
MN					
Yes	14(100.0)	0	1	2.400	0.121
No	45(84.9)	8(15.1)			
PIGN					
Yes	2(100.0)	0	1	0.280	0.597
No	57(87.7)	8(12.3)			
IgAN					
Yes	2(66.7)	1(33.3)	1	1.367	0.242
No	57(89.1)	7(10.9)			

glomerulonephritis (MPGN), and post infectious glomerulonephritis PIGN) were seen in 10 (14.90%), 8(11.90%) and 2(3.00%) of the study population respectively. IgA nephropathy was seen in 3 (4.5%) of the study population. Focal segmental glomerulosclerosis (FSGS), MN, PIGN and MPGN were seen more in age group 18-44years. In age group 45-60 years, the predominant histological diagnoses were FSGS and MN with the latter accounting for 60% of the diagnosis.

There was male preponderance across the histological pattern except in PIGN, MCD and MPGN where there was equal sex distribution. The distribution of the histological diagnosis across clinical syndromes is shown in figure 2. The pattern of biochemical changes across the different histological diagnosis is shown in table 3. Statistically significant relationship exists between serum creatinine > 132µmol/l (OR-8.673, 95% CI=1.60-46.7, Wald = 6.284, p = 0.012) and FSGS compared to other histologic diagnosis on simple logistic regression. There was statistically higher frequency of proteinuria (x^2- 6.635, df-1, p value-0.010) in patients with MCD (70%) when compared with those without MCD (28.1%) as shown in table 4.

DISCUSSION

This study is unique evaluated the clinicopathologic patterns of glomerular diseases in a homogeneous black population and correlated the patterns across different histological diagnosis. Majority of the study population were in the age range of 18-44 years which is similar to earlier reports by Chijioke et al and more recently by Umeizudike *et al*.[7,8] The higher occurrence of glomerulonephritides in young individuals have also been reported in other countries in Africa which is at variance with the findings on glomerulonephritides which occurs more among older individuals in the western world. [1,4,9,10,11,12]

Even though the majority of the patients in our study were males (67.2%), it was not statistically significant. Some studies reported no gender predisposition to GN[8] while others reported one sex predilection or the other [7,11,12]. The male preponderance observed in our study may be due to consecutive recruitment of patients into the study.

The passage of frothy urine was the most common clinical presentation seen in 95.5% of our study population closely followed by generalized body swelling. Hypertension (29.9%) and oliguria (14%) were seen in higher proportion of these patients compared with previous reports though occurrence

of haematuria was comparable with that reported by Umeizudike et al.[8] In this study, the mean daily protein excretion, serum albumin, total cholesterol and PCV were higher when compared to the findings of Umeizudike *et al.*[8] Nephrotic syndrome was the predominant clinical indication for renal biopsy in 41 patients (61.2%) with male preponderance which is comparable to documented reports from various studies in the country though in varying proportions.[6,7,8.]

Earlier work by Oviasu *et al*[6] in Southern Nigeria found nephrotic syndrome to be the commonest indication for renal biopsy which was also confirmed more recently by Umeizudike *et al.*[8] In Nigeria, nephrotic syndrome constitutes 2.4% of medical admissions.[7] Nephritic syndrome accounted for 13.4% of the indication for renal biopsy in this study which is close to 12.0% reported by Barsoum *et al*[13] in Egypt but higher than 5.8% reported by Okpechi *et al*[27] in South Africa. The differences observed might be due to better health seeking attitude, robust government participation in quality free health services from primary to tertiary level and availability and accessibility of health insurance scheme. All these factors possibly contributed to the prompt treatment of infectious causes of glomerular diseases. Similarly, geographical variation of glomerular diseases may also affect its pattern of presentation.[5]

Asymptomatic urinary abnormalities and haematuria were the least observed clinical presentation necessitating renal biopsy seen in 2% and 1% of the study population respectively. The low number of biopsies performed for patients with AUA may be reflective of the poor health seeking behaviour of our people in this part of the world as it is usually picked during routine medical examination.[1] Umeizudike et al[8] found AUA in 4% of their study population. In Europe and some parts of Africa, AUA and haematuria accounted for a large percentage of biopsies done as reported by Okpechi *et al*[2] in their study of primary glomerular diseases seen across Africa and Europe.

Statistically significant associations were seen between serum albumin, serum creatinine and the estimated GFR across the clinical syndromes. In addition, in this study, statistically significant association was seen between the clinical syndromes and the underlying histological diagnosis. This study agrees with the previously documented reports that clinical presentation in GN is dependent on the underlying histological diagnosis.[9,10] The degree of renal impairment across the clinical syndromes is dependent on the underlying histological diagnosis as progression to ESRD is more rapid in patients with FSGS compared to other non proliferative histological diagnosis.[1]

Using simple logistic regression, a statistically significant difference was observed in the serum creatinine values (>132μmol/L) between those with FSGS and those with other histological diagnoses with relatively high wald statistics of 6.284, odds ratio of 8.673 and a p value of 0.012. This clearly corroborates findings that patients with FSGS at the time of diagnosis may have impaired renal function with elevated serum creatinine.[1.6,7] There was however no statistically significant association between other histological patterns and biochemical parameters on simple logistic regression.

In our study, FSGS was the commonest histological diagnosis seen in 44.8% followed by MN seen in 14 patients (20.9%). Minimal change disease, MPGN, PIGN and IgA nephropathy accounted for 14.9%, 11.9%, 3.0% and 4.5% of the study population respectively. The commonest histological diagnosis in patients presenting with NS in this study was FSGS followed by MN, MPGN, MCD, PIGN and IgAN in that order. The finding of FSGS as the most frequent histological diagnosis compares favourably with that reported by Umeizudike *et al*[8] in Lagos but at variance to 19% reported by Chijioke *et al*[7] in Ilorin. The findings in our study is a clear deviation from previously reported pattern in local studies showing significant increase in the prevalence of FSGS and declining prevalence of proliferative GN. Oviasu *et al*[6] in 1992 found the frequency of FSGS to be 27.6% which is in sharp contrast to 44.8% reported in this study. In Kenya FSGS accounted for 15.2% of the pattern of GN coming a distant third after proliferative GN and MCD as reported by Mcligeyo *et al.*

Immunoglobulin A nephropathy was seen in 4.5% of the study population which was higher than the 3% earlier reported by Umeizudike *et al*[8] but lower than 33.3% reported by Oviasu *et al*[6] in 1982 in Benin[12]. In South Africa, the most common histological pattern of GN reported by Okpechi *et al*[11] was membranoproliferative GN while FSGS accounted for just 10.5%. This change in the pattern

of glomerular disease observed could be due to progressive decline in the incidence of infectious diseases in the tropics with effective antibiotic therapy, increase occurrence of non-communicable diseases such as obesity as well as influence of genetic factors.[6,7]

Although recent identification of Apolipoprotein L1 (APOL 1) gene mutation which is of high prevalence among the Yoruba's in South Western Nigeria has been linked with increased predisposition to FSGS with hastened progression to ESRD, the increase occurrence of FSGS in our study population will need further evaluation to identify possible association with APOL 1 gene polymorphism.[14] Post infectious GN was seen in 2 patients (3.0%) despite taking adequate history to exclude secondary causes of GN although serum level of Anti-Streptolysin O and anti deoxyribonuclease (DNase) were not assayed.

There was no statistically significant correlation between the biochemical parameters and the various histological patterns in this study although a weak correlation was observed between age and membranous GN. This finding may explain the varying incidence of different histological patterns in different ages. Renal function impairment in patients with GN depends on the acute nature of the illness and /or histological diagnosis. There were no statistically significant differences in the estimated GFR and serum creatinine across histological patterns in our study although subtle variations were observed across histological types.

Furthermore, this study found that patients with other histological lesions (71.9%) apart from MCD were more likely to have proteinuria, haematuria and or cast in their urine. Isolated proteinuria on urinalysis was significantly higher in patients with MCD than those without MCD. This finding is in agreement with earlier documentation that MCD being a non-proliferative GN usually causes proteinuria with haematuria being very rare.[9,10]

One of the limitations in this study includes the fact that it was hospital based and hence the low number of patients with asymptomatic urinary abnormalities and less severe disease. In this study only two (2) patients had AUA as their indication for renal biopsy. Larger studies possibly multicentre will be better powered to answer some of the evolving research questions. The cross-sectional nature of this study only favours a single point assessment of the biochemical parameters which makes prognostication as well as documentation of rate of progression difficult.

In conclusion, nephrotic syndrome is the predominant pattern of presentation necessitating renal biopsy in this environment. Statistically significant association were seen between the serum albumin, serum creatinine, serum cholesterol and the estimated GFR across the clinical syndromes. Focal segmental glomerulosclerosis was the commonest histological lesion found which is consistent with recent findings of the changing spectrum of primary GN in this environment. There was statistically significant association between pattern of presentation and underlying histologic diagnoses with patients presenting with FSGS more likely to have elevated serum creatinine when compared to other histologic patterns. Also, there was a statistically significant correlation between age and histologic diagnosis of MN. Renal biopsy still remains a cornerstone in the management of GN and the practise of nephrology world-wide. Chronic kidney disease is still a huge burden world-wide. Glomerulonephritis contributes a major percentage to the rising prevalence of end stage renal disease (ESRD) particularly in developing countries including Nigeria. Since the cost of renal replacement therapy is very high, routine and periodic urinalysis to screen for proteinuria and or haematuria for early diagnosis and prompt intervention in patients with AUA should be encouraged. The cost of renal biopsy should be subsidised by government through provision of health insurance to allow for thorough investigation of patients with suspected glomerulonephritis. Immunofluorescence and electron microscopy should be developed to be able to fully appraise renal histopathological lesions.

A larger community-based study with thorough and detailed histological evaluation of patients is needed to establish the true prevalence of primary glomerular disease in this environment.

Acknowledgement- nil

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