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ORIGINAL ARTICLE

Glomerular Density in the Renal Biopsies of patients with Focal Segmental Glomerulosclerosis: A Single Center Study

MUHAMMAD FAHAD FAIZ[1], MUDDASAR HUSSAIN[2], AURANGZEB AFZAL[3], USMAN HASSAN[4], MARYAM HAMEED[5], SHEEBA ISHTIAQ[6]

[1,2,4,5]*Department of Histopathology, Shaukat Khanum Memorial Cancer Hospital& Research Centre, Lahore*
[3]*Department of Nephrology, Services Institute of Medical Sciences, Lahore*
[6]*Department of Histopathology, Gulab Devi Hospital, Lahore*
Correspondence to Dr. Muhammad Fahad Faiz, E-mail: eem4you@hotmail.com Cell: 0333-8693191

ABSTRACT

Background: Generally, focal segmental glomerulosclerosis has a poor prognosis. It often progresses to end stage renal disease. Several clinical parameters are under research to define the prognosis and progression of the disease to end stage renal disease so that early treatment is given.
Aim: To correlate the glomerular density with different variants of focal segmental glomerulosclerosis and its association with the outcome of a disease.
Methods: Retrospective cohort study. Department of Histopathology, ShaukatKhanum Hospital and Research Center, Lahore from 1st January 2018 to 31st December 2020. One hundred and fifty five cases of focal segmental glomerulosclerosis as confirmed first by histology and then by immunofluorescence methods (IHC) and patients were enrolled. The biopsied tissues were embedded in paraffin and cut into 3-4 mm sections. Global glomerulosclerosis was defined when the entire glomerulus was involved in sclerosis, and segmental sclerosis was defined when part of the glomerulus was sclerosed. Interstitial fibrosis was defined when there was increased extracellular matrix separating tubules in the cortical area.
Results: The mean glomerular density was 2.2±4. A lower glomerular density (<3/mm^2) was associated with higher urinary protein excretion and lower estimated glomerular filtration rate. There were more patients in this group who had hypertension. The lower glomerular density was however, associated with lesser global and segmentally sclerosed glomeruli. More patients (80%) had to undergo either transplant or dialysis.Over half of patients (62.6%) were hypertensive, with only 24.5% receiving dialysis or transplant. Most were treated with medical therapy, with 74% receiving steroids. The mean follow-up time was 24±18 months, and most biopsies showed NOS variants. Almost 21% had remission, while 65% had relapse. Patients with higher glomerular filtration rate (GD) had higher eGFR and UPE.
Practical implication: Pakistan's hilar type of focal segmental glomerulosclerosis (FSGS) has worse outcomes due to its lowest glomerular density. Improving pathology evaluation, training, and knowledge is crucial for prompt diagnosis and treatment. Customizing treatment regimens based on FSGS and glomerular density, improving healthcare resource distribution, and promoting public health campaigns can help prevent end-stage renal disease.
Conclusion: Glomerular density is lowest in the hilar type of focal segmental glomerulosclerosis followed by not otherwise specified, tip, and collapsing variants of focal segmental glomerulosclerosis. The lower glomerular density patients have a worse outcome and require dialysis more often. Hence, patients with these variants should be treated more aggressively and their glomerular density can be used for prognosis.
Keywords: Focal segmental glomerulosclerosis (FSGS), Renal biopsy, glomerular density (GD), urinary protein excretion (UPE)

INTRODUCTION

Focal segmental glomerular sclerosis (FSGS) is represented by an increase in the glomerular mesangial matrix and destruction of the capillary lumina of at least one glomerulus in a biopsy of an entire kidney. There are various etiologies and mechanisms behind the histological changes but one feature that starts and defines the process isthe alteration and effacementof podocyte foot processes(podocytopathy)[1]. In some studies, the FSGS accounts for 16.8% of cases of nephrotic syndrome in the Polish population while the same affects 12.3% of patients of nephrotic syndrome in Italy[2]. In Pakistan, FSGS affects almost 40% of nephrotic patients[3].

Focal segmental glomerular sclerosis may be divided into primary and secondary FSGS. It is called primary when the kidney biopsy reveals the characteristic lesions in the presence of nephrotic syndrome, serum hypoalbuminemia and with no identifiable cause. Focal segmental glomerular sclerosis may progress to end-stage renal disease in a subset of patients, requiring renal replacement therapy. FSGS accounts for almost 2% of adult cases of ESRD[4].

Focal segmental glomerular sclerosis has five histological variants: perihilar, cellular, tip, collapsing and not otherwise specified (NOS). The collapsing variant shows the worst prognosis, almost 70% of patients having this variant progress to ESRD[5]. The most important clinical feature is proteinuria of different extents that may or may not be associated with nephrotic syndrome[6].

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Several factors have been identified to date which affects the progress of the disease into ESRD. The estimated glomerular filtration rate (eGFR) and 24-hour urinary protein excretion (UPE) have been known to be important risk factors defining the prognosis of disease[7]. One such entity is the glomerular density (GD). There is a paucity of data on the association of glomerular density (GD) with FSGS subtypes and also its clinical correlation. One study has shown the association of low birth weight with glomerular density and it has been associated with defining the prognosis of IgA nephropathy patients[8].

The objective of this study is to find out the clinicopathological features of FSGS in our population and also to co-relate its association with GD as an independent risk factor.

PATIENTS AND METHODS

This retrospective cohort study was conducted at the Department of Histopathology, Shaukat Khanum Hospital and Research Center, Lahore. The patients selected were diagnosed FSGS patients diagnosed between 2018 and 2020. All cases of focal segmental glomerulosclerosis as confirmed first by histology and then by immunofluorescence methods (IHC) and patients who consent to study. All cases of FSGS that were inconclusive on histology and had other coexisting patterns of glomerular injury were excluded from the study. FSGS in the biopsies of renal transplant patients were also excluded. The sample size of this study came out to be 80. It was calculated using OpenEpi online calculator keeping 95% Confidence interval and 80% power of study[8]. However, we followed 155 patients.

The biopsies of all selected patients were taken by percutaneous method. The biopsied tissues were embedded in paraffin and cut into 3-4mm sections. They were stained using periodic acid–Schiff and periodic acid-methenamine silver. Global glomerulosclerosis was defined when the entire glomerulus was involved in sclerosis, and segmental sclerosis was defined when part of glomerulus was sclerosed. Interstitial fibrosis was defined when there was increased extracellular matrix separating tubules in the cortical area. The GD was determined by calculating the number of glomeruli that were not globally sclerotic per total renal cortical area4in square millimeter (mm^2). The data was entered and analyzed through SPSS 26. Chi-square test, independent sample t-test, and One-way Annova were applied. A p-value of ≤0.05 was considered statistically significant

RESULTS

More than half of patients (62.6%) were hypertensive. Only 24.5% of patients were given dialysis or transplant. Rest was treated with medical therapy only. The reason was almost 74% patients were given steroids (Tables 1). The mean follow-up time for these patients was 24±18 (9-204) months. The mean eGFR was 51±44. The maximum number of biopsies (71.6%) showed NOS variant of FSGS. Next were tip variant followed by cellular, collapsing and hilar variant. IF/TA was mild in most biopsies (42%). Almost 21% of patients had a remission while 65% had some degree of relapse (Table 2-3).The patients were divided into two groups depending upon their GD being lesser or greater than 3/mm^2. The patients with higher GD(>3/mm^2) had higher eGFR of more than 70±47 as compared to 3.3±5.5 (p=0.007).

Table 1: Demographic information of the patients (n=155)

Variable	No.	%
Gender		
Male	103	66.5
Female	52	33.5
Hypertension		
Yes	97	62.6
No	58	37.4
Dialysis requirement		
Yes	38	24.6
No	117	75.4
Steroid given		
Yes	116	74.8
No	39	25.2

Table 2: Descriptive statistics of the patients (n=155)

Variable	Mean±SD
Age (years)	30.3±14.9
eGFR	51±44
UPE (g/day)	3.2±5
GD (/mm^2)	2.2±1.4
Global glomerular sclerosis	1.3±3.3
Segmental glomerular sclerosis	3.6±2.4
Duration of treatment follow-up (months)	24±18

Table 3: Final results of the patients (n=155)

Variable	No.	%
Histopathological pattern		
Cellular	6	3.8
NOS	111	71.6
Hilar	3	1.9
Tip	33	21.3
Collapsing	2	1.4
IF/TA		
Absent	39	25.2
Mild	65	41.9
Moderate	51	32.9
Outcome		
Expired	21	13.5
Relapse	43	27.7
Partial remission	59	38.1
Remission	32	20.7

UPE of higher GD patients was 2.9±2.2 as compared to 3.3±5.5 of patients with lower GD. The higher GD patients had more glomeruli with global and segmental sclerosis (Table 4, Fig.1,2).

Table 4: Comparison of characteristics of FSGS patients with low and high GD

Characteristics	Low GD (<3/mm2) (n=123)	High GD (3/MM2) (n=32)	p-value
Clinical			
Mean age (years)	30±14	30±15	0.912
eGFR (ml/min/1.73m^2)	46±42	70±47	0.007
UPE (g/day)	3.3±5.5	2.9±2.2	0.672
Hypertension (%)	65.6	61.8	0.690
Histopathological			
Global glomerular sclerosis (n)	1.2±2	3.5±5	0.001
Segmental glomerular sclerosis (n)	3.3±2.1	5.0±2.8	0.000
Treatment			
Duration of follow-up months)	23±12	28±34	0.129
Dialysis requirement (yes)	89.5%	10.5%	0.07
Steroid given (yes)	75.6%	71%	0.66

Fig. 1: Glomerular density in IF/TA

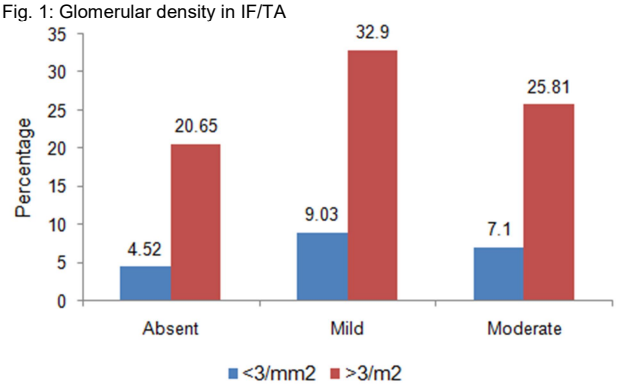
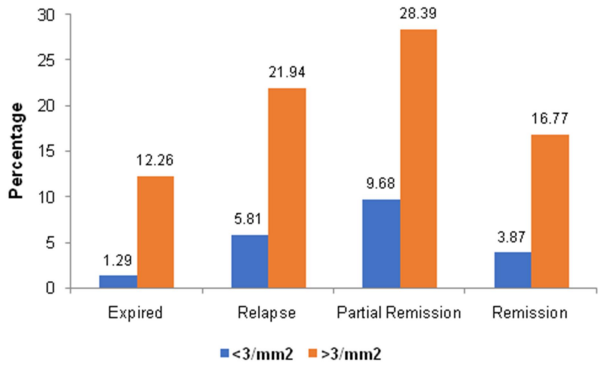


Fig. 2: Comparison of outcome of IF/TA and glomerular density



DISCUSSION

Focal segmental glomerulosclerosisis the most common glomerulonephritis in Pakistan (28%)[9]. It is an entity characterized by proteinuria, may or may not accompanied by nephrotic syndrome. The major pathologic finding is podocyte effacement. The majority of the cases have overlapping clinical and histological findings. Therefore, the exact diagnosis is a challenge, and the majority of them end up in ESRD even after immunosuppression. This requires either dialysis or transplantation[10]. Hence, being the major contributor to ESRD and the huge incidence in our population, the early prediction of the prognosis is crucial to control

the disease at an early stage. This study showed the prevalence of disease is more in males; almost 66.5%.

The mean age of presentation has been shown to be 30±14.9 years, but it can present in any age from 1 to 70 years. Our finding is different from the age prevalence of FSGS in Japan, which shows a median age of 54 years, however, the prevalence in gender is similar[11]. The mean eGFR of FSGS patients was 51±44 (5-184) ml/kg/min. The mean UPE was 3.2±5 g/day. Almost 63% of patients were hypertensive.

In this study, the most common type of FSGS is NOS (71%) followed by other variants. This is consistent with an American study that showed similar results[12]. The mean GD in FSGS patients was 2.2±1.4/mm^2. More glomeruli were sclerosed segmentally i.e., 3.6±2.4 as compared to globally sclerosed glomeruli 1.3±3.3. Forty-two percent had mild interstitial fibrosis and it was absent in 25% of patients. These results are consistent with Alhozali et al[13] which showed that there were more segmentally as compared to global sclerosis. In addition, there was mild as compared to moderate fibrosis. Steroids were given in 75% of patients while transplant/dialysis was required in 25% of patients. Twenty-one percent of patients had remission, 38.1% had partial remission, 27.7% had relapsed and 14% of patients expired during follow-up. Our results remained almost comparable to a study in Kaula Lumpur which showed remission in 28% of patients[14]. The decrease in glomerular density has shown to be related to other types of glomerulopathies too, including diabetes-induced and IgA nephropathies[15,16].

The GD varies in our study within different variants of FSGS. The lowest GD is in hilar type followed by NOS. This difference is statistically significant. Our study also shows that glomerular density is significantly associated with FSGS. That is the lesser the density, the more chances of FSGS having a worse prognosis. In other words, the lower glomerular density in our study was associated with hilar type; p-value 0.029. Similarly, in the collapsing variant, 2 patients were below 2/mm^3. So, the data has been stratified into two groups for the sake of convenience and lower densities of glomerulus less than 3 have even worse outcomes. The patients having higher GD (>3/mm^2) had lower UPE (2.9±2.2) as compared to patients having lower GD. Also, these patients had more segmentally as well as globally sclerosed glomeruli. This finding is due to the fact that more glomeruli are preserved in patients with higher GD hence more sclerosis. Only 11% of patients with high GD required dialysis or transplant as compared to 80% in patients with low GD. Hence, the patients with higher GD have a better prognosis than patients with lower GD. As NOS is the variant present in abundance and it has a low GD, so it should be given aggressive management as it can progress more frequently to a worse outcome. The IF/TA was irrespectively within mostly the mild range in all groups of glomerular density, whether it was below 1, above 1, or even above 3. This means that IFTA is independent of glomerular density and maybe it depends on the individual case. The patients with GD less than 1 had the least chance of remission. Remission was more common in patients with GD more than 2/mm^3. Expiries also occurred more in this group due to more patient numbers. but least remission in least glomerular density signifies a necessity to more aggressive management of such patients.

CONCLUSION

Glomerular density is lowest in the hilar type of focal segmental glomerulosclerosis followed by not otherwise specified, tip, and collapsing variants of focal segmental glomerulosclerosis. The lower glomerular density patients have a worse outcome and require dialysis more often. Hence, patients with these variants should be treated more aggressively and their glomerular densitycan be used for prognosis.

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1. Conception and design of or acquisition of data or analysis and interpretation of data.
2. Drafting the manuscript or revising it critically for important intellectual content.
3. Final approval of the version for publication.

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