Study of Prevalance of Nephropathy among Sickle Cell Disease Patients in Waghodia Region, Vadodara, Gujarat

Charmi C. Thakkar a# and Inampudi Sailaja b†

a Parul Institute of Applied Sciences, Parul University, Vadodara-391760, Gujarat, India.

b Department of Biochemistry, Parul Institute of Applied Sciences, Parul University, Vadodara-391760, Gujarat, India.

Authors’ contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Introduction: Sickle-cell disease (or drepanocytosis) is a life-long blood disorder characterized by red blood cells that assume an abnormal, rigid, sickle shape. Sickle cell disease (SCD) has several complications, including chronic renal failure, manifesting with hypertension (high blood pressure) proteinuria (protein loss in the urine), hematuria (red blood cells in urine) and worsening anaemia. Progression to end-stage renal failure confers a poor prognosis.

Objective: The objective of the study was to determine the Prevalence of Nephropathy among sickle cell disease patients.

Materials and Methods: This cross sectional study includes a total 150 participants who suffering from sickle cell anemia and attending our Institute. Renal function test and Urine examination of all participants was done. Estimated Glomerular Filtration Rate (eGFR) calculated using the Cockroft Gault formula. Comparison of results was done between Sickle cell trait and Sickle cell disease Group.

Results: The mean age of the SCA patients were 25.54±10 years. Maximum participants are found to be from age group 25-30 y(n=35) followed by 20-25 y(n=30). Of the 150 SCA patients, 89 (59.33%), and 61 (40.66%) were males and females, respectively. The Mean value of S.Creatinine

# PhD Scholar;
† Assistant Professor;
*Corresponding author; E-mail: appliedbio11111@gmail.com;
The mean value of albuminuria in the general population may represent hypertension in SCD patients [8-9].

Kidney involvement in sickle cell disease (SCD) includes a variety of glomerular and tubular disorders, which are associated with increased mortality [10-11]. The pathophysiology of sickle cell nephropathy (SCN) is related to the normal medullary environment which is characterized by low oxygen tension, low pH, and high osmolality, these conditions in SCD patients predispose to red blood cell sickling [12]. SCD affects the kidney by acute mechanisms, as a form of the sickle crisis and insidiously with renal medullary/papillary necrosis, with resulting tubular defects. SCD is associated with many functional and structural abnormalities of the kidney which may progress to end-stage renal disease [13]. This study, therefore, attempt to determine the prevalence and pattern of biochemical renal function tests and their relationship sickle cell anemia (SCA) patients in Waghodia region of Gujarat.

2. MATERIALS AND METHODS

This cross sectional study was conducted at Parul Institute of Applied Sciences in collaboration with Parul Sevashram Hospital, Vadodara, Gujarat from 2017-2018.

Inclusion Criteria: Sickle cell disease patients already diagnosed by any of the confirmatory method like Hb gel electrophoresis, capillary electrophoresis and genetic analysis along with investigated for Urine routine microscopy and Serum Creatinine and aged 5 years and above will be considered for enrolment.

Sample size: The sample size will be 150 already diagnosed Sickle cell disease patients.

2.1 Data Collection

Data collection of following parameters will be done
Specimens and Investigations: Blood samples for Renal function test (RFT) was collected aseptically in 5 ml red top vaccutainers.

All samples were centrifugated at central laboratory in REMI centrifuge at 3000 RPM and serum was separated.

About 10 ml of mid-stream urine will be collected in universal sterile clear bottles for urine analysis. Young children were assisted by their accompanying parents/guardians on collecting the midstream urine, where they were instructed to wait a few seconds as the child starts voiding, then collected the urine.

Serum creatinine will be performed in the laboratory using fully automated biochemistry analyser along with Quality control material. Urinalysis was done macroscopically using urine dipstick and microscopy using microscope. Estimated Glomerular Filtration Rate (eGFR) was calculated using the Cockroft-Gault equation/formula. eGFR of less than 60mL/min/1.73m2 was described as established renal failure.

Proteinuria in patients with eGFR>90 will be defined as stage one renal failure.

3. RESULTS

The mean age of the SCA patients was 25.54±10 years (Table 1). Maximum participants are found to be from age group 25-30 yr(n=35) followed by 20-25 yr(n=30). Of the 150 SCA patients, 89 (59.33%), and 61 (40.66%) were males and females, respectively.

Table 1. Demographic characteristics of participants

| Age Group(yr) | Number(n) |
|---------------|-----------|
| 5-10 yr       | 20        |
| 10-15 yr      | 20        |
| 15-20 yr      | 25        |
| 20-25 yr      | 30        |
| 25-30 yr      | 35        |
| 30-35 yr      | 20        |
| Total         | 150       |

Graph 1. Graphical distribution of participants according to age group
Table 2. Distribution of participants based on type of sickle cell anemia (SCA)

| Total | Sickle cell trait (SCT) | Sickle cell disease (SCD) |
|-------|------------------------|--------------------------|
| 150   | 92 (61.33%)            | 58 (38.66%)              |

Table 3. Gender wise distribution of participants

| Total | Gender Ratio |
|-------|--------------|
| 150   | Male: female |
|       | 89:61        |

Table 4. Renal Parameters of SCT and SCD patients

|                    | S.creatinine (mg/dl) | U. Albumin | eGFR (ml/min) |
|--------------------|-----------------------|------------|---------------|
| Sickle cell Trait  | 0.73 ± 0.46           | NIL        | 134.19 ± 87.21|
| Sickle cell Disease| 1.0 ± 0.35            | +1         | 124.20 ± 58.25|

Table 5. Comparison of biochemical Results between SCT and SCD patients by calculating p – value

|                    | S. creatinine (mg/dl) | eGFR (ml/min) | p- value |
|--------------------|-----------------------|---------------|----------|
| Sickle cell Trait  | 0.73                  | 134.19 ± 87.21| <0.05    |
| Sickle cell Disease| 1.0                   | 124.20 ± 58.25| <0.05    |

(\(P\) value <0.05 considered as a significant)

The Mean value of S. Creatinine of SCT group is 0.73 ± 0.46 mg/dl and SCD is 1.0 ± 0.35 mg/dl, while the Mean value of eGFR is 134.19 ± 87.21 ml/min and 124.20 ± 58.25 ml/min in SCT and SCD Group respectively (Table 4).

In SCD group, urine Examination shows Protein Level +1 while in SCT group does not find protein in urine.

There is significant difference found in level of serum creatinine between SCT and SCD group and p value is <0.05. in eGFR also we got significant difference between two group (Table 5).

4. DISCUSSION

In this study, the pattern of biochemical renal function tests and relationship with eGFR was evaluated in SCA patients in the steady state, and the results clarify important aspects of tubular and glomerular dysfunction in these patients.

Kidney disease is a common complication in sickle cell anemia (SCA), which leads to increased morbidity and early mortality. The National Kidney Foundation guidelines use an estimated glomerular filtration rate (eGFR) cutoff of 60 mL/min/1.73m² to define chronic kidney disease (CKD). However, many SCA patients have an elevated baseline eGFR due to low serum creatinine levels from reduced muscle mass, abnormal tubular secretion of serum creatinine into the urine, and/or high cardiac output from the hemolytic anemia [14]. The standard definition of CKD may represent a greater decline from "normal" kidney function in SCA patients compared to the general population.

The reduced GFR observed during VOC in this study, and those of others [15-16] may be attributable to glomerular microvascular occlusion by sickled erythrocytes and several other events, which are well known to occur during VOC (vasoocclusive crisis) [17]. Furthermore, the stress and pain associated with vasoocclusive crisis may give rise to an increase in the sympathetic discharge and a rise in the level of blood anti-diuretic hormone and adrenalin (causing mesangial cells contraction) with a resultant decrease in the GFR [18].

The cumulative effect of all these factors (glomerular occlusion and contraction of mesangial cells) is a reduction in the effective surface area available for filtration and hence the reduced GFR observed during VOC. A search into the literature did not show that much work had been published on the effect of hyperhemolytic crises on the GFR of children with the SCD even though hyperhemolytic crises have been identified as a major cause of hospitalizations in one study. However, the major pathogenetic mechanism...
operating in hyperhemolytic crises is that of acute exacerbation of hemolysis on chronic hemolytic process resulting in more severe anemia than what is obtained in the steady state. This study showed that there was an observed reduction in the mean GFR during hyperhemolytic crises with a statistically significant improvement in the mean GFR following recovery into the steady state. Although circulatory adjustments to anemia had increased the cardiac output and increased renal blood flow (i.e., increased GFR), blood is eventually diverted away from the kidney to other organs like the heart, the brain, and the adrenals which are more susceptible to hypoxia [19-20]. Consequently, the hypoxic injury of the acute anemic state may cause glomerular endothelial damage with a resultant reduction in the effective filtration surface area and hence the observed reduction in GFR as found in the present study.

Sickle cell nephropathy is a spectrum of changes resulting from a cascade of events occurring in the kidney. This is triggered by red blood cell vascular occlusion, infarction and reperfusion injury occurring within the renal medullar, cortex and collecting system. These may present as hyperfiltration, impaired urinary concentrating ability, albuminuria, decreased eGFR and end stage kidney disease [21-22]. Chronic sickle cell anemia is based on multiple kidney injury mechanisms: O2 depression on the side of the renal capillaries arteries; high blood pressure and low pH in the kidney and brain promote the formation of hemoglobin polymers in red blood cells, sickle cell deformation, resulting in increased blood viscosity and function Sexual venous congestion and interstitial edema make the renal microcirculation prone to ischemia and infarction [23]. The occlusion of bone marrow blood vessels leads to segmental scar formation and interstitial fibrosis (structural papillectomy), which leads to dilation of renal pelvic veins and capillaries. Hematuria may be due to early venous congestion leading to rupture of blood vessels or vasodilation caused by scarring. The development of collateral vessels and their abnormal orientation in the medulla disrupted the countercurrent exchange mechanism and reached its peak within many years accompanied by irreversible loss of bone marrow tone [24]. The increase in cortical renal blood flow and GFR may be due to the secretion of prostaglandins, which dilates bone marrow blood vessels. Excessive filtration and glomerular hypertrophy can lead to glomerular sclerosis [25].

Vincent Audard et al. [26] Found that the occurrence of proteinuria in sickle cell disease patients has increased greatly over last decade. However, the assessment of other robust biomarkers before the onset of micro albuminuria and/or GFR deterioration is desirable, to help clinicians to detect SCD patients at risk of renal damage early and to identify patients with a subsequent risk of renal disease progression.

The reduced GFR observed during in this study, and those of others [27-28] may be attributable to glomerular microvascular occlusion by sickled erythrocytes and several other events, which are well known to occur during SCD [29]. Furthermore, the stress and pain associated with vasocclusive crisis may give rise to an increase in the sympathetic discharge and a rise in the level of blood anti-diuretic hormone and adrenalin (causing mesangial cells contraction) with a resultant decrease in the GFR.

Joanne Thompson et al. [30]. Found that GFR remained within reference range or elevated in patients with SC disease aged 18 to 23 years. The higher GFR in patients with albuminuria was consistent with the hypothesis that high glomerular flows cause renal damage. Lower serum creatinine levels characterize patients with SS disease, and a revised clinical definition based on serum creatinine level alone is proposed.

Our study had both strengths and limitations. The strengths are, our study is planned with good number of samples selected from homogenous population of central India and all the participants were from single center. Our study participants comprise all age groups. In spite of these advantages, the present study also has a number of limitations. The results of this study are limited by the cross- sectional design. Subsequently, this information could be useful in assessing the risk factors to CKD advance- ment in SCD. Thus, it is recommended that a longitudinal study to characterize the progression of CKD for early therapeutic intervention to control the morbidity and mortality associated with SCD.

5. CONCLUSION

From our study we would like to conclude that derangement of Kidney function in sickle cell disease is frequent in our setting especially among young adult. It concerns SCD as well as SCT patients. Albuminuria is more frequent in
homozygote patients and its prevalence increase with age. Age ≥ 25 years is associated with high risk of CKD in SCA group and albuminuria in SCD.

CONSENT

As per international standard or university standard, patients’ written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Platt OS, Brambilla DJ, Rosse WF, et al. “Mortality in sickle cell disease. Life expectancy and risk factors for early death”. N. Engl. J. Med. 1994;330(23):1639-44.
2. Ashley-Koch A, Yang Q, Olney RS. Hemoglobin S Allele and Sickle Cell Disease.”American Journal of Epidemiology. 1998;151(9):839-45.
3. Powars DR, Elliott-Mills DD, Chan L, et al. Chronic renal failure in sickle cell disease: risk factors, clinical course, and mortality”. Ann. Intern. Med. 1991;115(8):614–20.
4. Colah RB, Mukherjee MB, Martin S, Ghosh K. Sickle cell disease in tribal populations in India. Indian J Med Res. 2015;141:509-15.
5. Mukherjee MB, Lu CY, Ducrocq R, et al. Effect of alpha-thalassemia on sickle-cell anemia linked to the Arab-Indian haplotype in India. Am J Hematol. 1997;55:104-9.
6. Hirschberg R. Glomerular hyperfiltration in sickle cell disease. Clin J Am Soc Nephrol. 2010;5(5):748–749. Comment on: Clin J Am Soc Nephrol. 2010;5(5):756-61.
7. Guasch A, Navarrete J, Nass K, Zayas CF. Glomerular involvement in adults with sickle cell hemoglobinopathies: prevalence and clinical correlates of progressive renal failure. J Am Soc Nephrol. 2006;17(8):2228–2235.
8. deribigbe A, Arieje A, Akinkugbe OO. Glomerular function in sickle cell disease patients during crisis. Afr J Med Sci. 1994;23:153-60.
9. Ocheke P. The effect of vasoocclusive crisis on the glomerular filtration rate of children with sickle cell anemia. Dissertation for fellowship of the West African College of Physicians; 1998.
10. Steinberg MH. Predicting clinical severity in sickle cell anemia. Br J Haematol. 2005;129:465-81.
11. Steinberg MH. Sickle cell anemia, the first molecular disease: Overview of molecular etiology, pathophysiology, and therapeutic approaches. Scientific World Journal. 2008;8:1295-324.
12. Silva Junior GB, Vieira AP, Couto Bem AX, Alves MP, Meneses GC, Martins AM, et al. Renal tubular dysfunction in sickle cell disease. Kidney Blood Press Res. 2013;38:1-10.
13. Marouf R, Mojmimiyi O, Abdella N, Kortom M, Al Wazzan H. Comparison of renal function markers in Kuwaiti patients with sickle cell disease. J Clin Pathol. 2006;59:345-51.
14. Addae S. Aspect of renal function in sickle cell crises. Ghana Med J. 1972;3:242.8.
15. Aderibigbe A, Arieje A, Akinkugbe OO. Glomerular function in sickle cell disease patients during crisis. Afr J Med Sci. 1994;23:153-60.
16. Konotey-Ahulu FI. The sickle cell diseases. Clinical manifestations including the "sickle crisis". Arch Intern Med. 1974;133:611-9.
17. Maharajan R, Fleming AF, Egler LJ. Pattern of infections among patients with sickle cell anemia requiring hospital admission. N. Engl. J. Med. 1983;130:10-7.
18. Sergeant GR. The clinical picture of sickle cell disease. Bailliere's clin Haem. 1993;6:93-115.
19. Silva AB da, Molina M del C, Rodrigues SL, Pimentel EB, Baldo MP, Mill JG. Correlation between the creatinine clearance in the urine collected during 24 hours and 12 hours. J Bras Neurol. 2010;32(2):165–172.
20. Ataga KI, Orringer EP. Renal abnormalities in sickle cell disease. Am J Hematol.2000;63(4):205–211. Comment on: Am J Hematol. 2001;66(1):68-9.
21. Alleyne GA, Status van Eps LW, Addac SK, Nicholson GD, Schouten H. The kidney in sickle cell anaemia. Kidney Int. 1975;7:371-9.
22. McCrory WM. Measurement of renal function during growth in infancy and childhood. In: McCror WM, editor. Developmental Nephrology. Havard: Cambridge Press. 1972;95-108.

23. Kaul DK, Nagel RL, Chen D, Tsai HM. Sickle erythrocyte-endothelial interactions in microcirculation: The role of von Willebrand factor and implications for vasoocclusion. Blood. 1993;81:2429-38

24. Silva AB da, Molina M del C, Rodrigues SL, Pimentel EB, Baldo MP, Mill JG. Correlation between the creatinine clearance in the urine collected during 24 hours and 12 hours. J Bras Nefrol. 2010;32(2):165–172.

25. Kon V, Karnovsky MJ. Norepinephrine decreases planar surface of rat mesangial cell. Kidney Int. 1987;31:424

26. Vincent Audard, Pablo Bartolucci and Thomas Stehle. “Sickle cell disease and albuminuria: recent advances in our understanding of sickle cell nephropathy”. Clin. Kidney Journal. 2017;10(4):475-478.

27. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

28. Kara LL, Wu AH. Renal function. In: Micheal LB, Edward PF, Larry ES, editors. Clinical Chemistry Techniques, Principle, Correlations. 6th ed. Lippincott, USA: Williams and Wikins. 2010;574.

29. Nduka N, Kazem Y, Saleh B. Variation in serum electrolytes and enzyme concentrations in patients with sickle cell disease. J Clin Pathol. 1995;48:648-51.

30. Joanne Thompson et al. “Albuminuria and renal function in Homozygous Sickle cell disease”. Arch Intern Med. 2007;167.

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