

Original Research Article

STUDY OF PREVALANCE OF NEPHROPATHY AMONG SICKLE CELL DISEASE PATIENTS IN WAGHODIA REGION, VADODARA, GUJARAT

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 Cockcroft 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 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. 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.

Conclusions: From our study we conclude that **the** 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.

Key Words: Sickle cell, Nephropathy, Creatinine

INTRODUCTION

Sickle cell disease (SCD) and its variants are genetic disorders resulting from the presence of a mutated form of hemoglobin.^[1,2] Renal disease is one of the most frequent complications, and kidney damage starts very early and progresses throughout life causing severe complications. India is estimated to be home to over 50% of the global SCD patient population. Although the exact reason is not known, the HbS gene is mainly concentrated in scheduled tribal, scheduled caste, and other backward caste populations of Madhya Pradesh, Orissa, Chhattisgarh, Jharkhand, Gujarat, Andhra Pradesh, and Kerala states where carrier frequencies range between 5% and 40% or more^[3,4]. Sickle cell disease is very common in rural population in Vadodara district around Waghodia taluka. The World Health Organization has recognized that Sickle cell disease (SCD) as a problem of major public health significance^[5].

The main mechanism of kidney injury or sickle cell nephropathy (SCN) is mainly related to hypoxia and ischemia. The clinical manifestations are determined by the main location of renal tubular lesions. The ascending branches of the kidney loops reabsorb dissolved substances, impairing the ability of urine to concentrate. Distal renal tubular dysfunction can change kidney acidity and potassium secretion, leading to incomplete distal renal tubular acidosis and hyperkalemia. The blood pressure of , SCD patients is generally lower than that of healthy, healthy patients, and hypertension only occurs in 26% of patients.^[6,7] The low incidence of hypertension is attributable to decreased vascular reactivity, compensatory systemic vasodilation associated with microvascular changes associated with red blood cell formation and thrombotic complications, elevated prostaglandin and nitric oxide levels, and sodium in the kidneys The loss of water and water may not be enough for the bone marrow to focus. Therefore, blood pressure defined as normal 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.

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.

Data collection

Data collection of following parameters will be done

1. Age, sex and weight of the patients
2. Urine routine microscopy report
3. Serum creatinine level
4. GFR or estimated creatinine clearance will be calculated by formula and patients will be classified according to GFR having renal failure or not.

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times \text{Constant}}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

The formula, as originally published for creatinine in $\mu\text{mol/L}$.

Where Constant is 1.23 for men and 1.04 for women.

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 Cockcroft-Gault equation/formula. eGFR of less than 60mL/min/1.73m² was described as established renal failure.

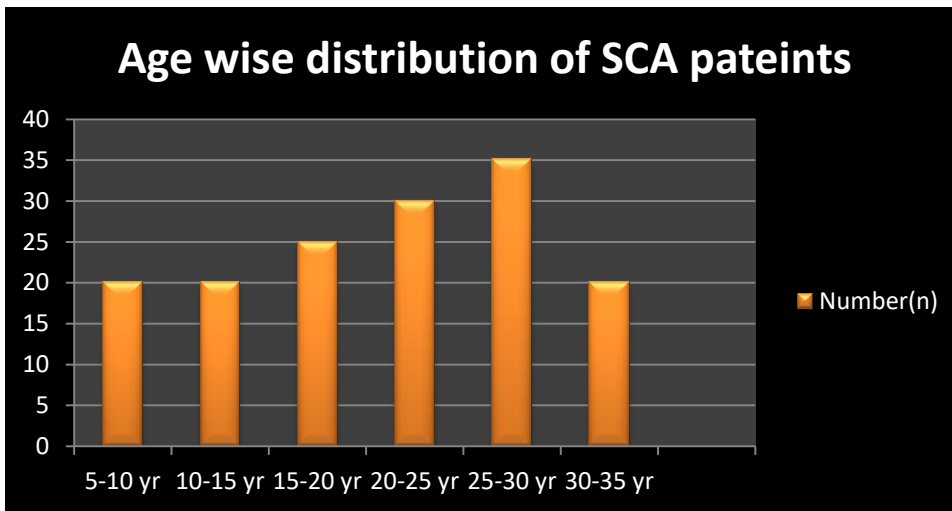
Proteinuria in patients with eGFR>90 will be defined as stage one renal failure.

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.

| 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 |

Table 1: Demographic Characteristics of participants



Graph 1: Graphical Distribution of participants according to Age group

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

Table 2: Distribution of participants Based on type of sickle cell anemia (SCA)

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

Table 3: Gender wise distribution of participants

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

Table 4: Renal Parameters of SCT and SCD patients

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.

| | <i>Sickle cell Trait</i> | <i>Sickle cell Disease</i> | <i>p- value</i> |
|-----------------------------|--------------------------|----------------------------|-----------------|
| <i>S. creatinine(mg/dl)</i> | 0.73 | 1.0 | <0.05 |
| <i>eGFR(ml/min)</i> | 134 | 124 | <0.05 |

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

(P value <0.05 considered as a significant)

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)

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 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.

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 advancement 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.

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.

Ethical Approval:

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

Consent

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

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