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Renal Impairment in Sickle Cell Disease

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Abstract
Introduction and objectives: *Sickle cell disease is the most common structural haemoglobin disorder in the world. Despite its apparently simple molecular aetiology, sickle cell disease has long been known to have remarkably variable clinical course, with complications involving many organs including the kidneys. This study was performed to find out the various renal impairment in SCD, to record their frequency and severity with observation of any decline in GFR with progress of time and to identify factors if any that accelerates its progression.*
Material and methods: *50 patients of SCD who satisfied the inclusion and exclusion criteria were included in the study and were assessed for presence of renal impairment with complete clinical examination, laboratory investigations which includes CBC,blood urea, serum creatinine,seum electrolytes,urine examination,24 hours urine protein, urine microalbumin, imaging study of kidney and followed up with serial blood urea, serum creatinine and eGFR values.*
Results: *Out of 50 patients 72% were male and 28% female. The mean age was 36.18 years with 64% in the age group of 26-45 years. The most common symptom was painful episodes (70%) and pallor was the most important clinical finding in 92% of patients. Splenomegaly was the most common finding on systemic examination. The mean serum fetal haemoglobin was 17.76%. Hematuria was detected in 10% and pyuria in 24% of patients. Most of the patients (62%) had proteinuria within 150-500 mg/day while 6% cases having nephrotic range proteinuria. Microalbuminuria was found in 74% of patients with 16% showing macroalbuminuria. Their was a progressive decline in the eGFR value with a rise in blood urea and serum creatinine level with the progress of study till end. The decline in mean eGFR was nearly 10ml/min/1.73m^2. The USG of kidney showed a normal size in 80% of patients.*
Conclusion: *Sickle cell nephropathy is one of the important cause of deterioration in renal function in patients attending our institute with an early age of involvement. The eGFR had a significant decline as the time progress in patients of SCD with renal impairment. Fetal haemoglobin may have a protective role in sickle cell nephropathy.*

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I. Introduction

Sickle cell disease is the most common structural haemoglobin (Hb) disorder in the world. It comprises of a group of inherited haemoglobin disorders that include sickle cell anaemia (HbSS), sickle cell trait (AS), and compound heterozygous states like sickle cell β-thalassemia (HbSβ), sickle cell D Punjab (HbSD Punjab), HbSE, HbSC, etc characterized by sickling of erythrocytes when they are deoxygenated. The term sickle cell disease (SCD) refers to a group of symptomatic genetic haemolytic anemias in which the erythrocytes have a predominance of sickle haemoglobin (HbS) due to inheritance of a β-globin mutation (βS) and includes homozygous or compound heterozygotes states of haemoglobin S (HbS). The Hb variants results from single aminoacid substitution in alpha and beta chains. HbS results from glutamic acid to valine substitution at 6th position of beta globin chain[1].

Affected individuals typically are homozygous for the sickle cell mutation (HbSS) or have a compound heterozygous state (eg, HbSC, HbS β-thalassemia). The βS mutation creates a hydrophobic region that, in the deoxygenated state, facilitates a noncovalent polymerization of HbS molecules which has the potential to damage the erythrocyte membrane and can change the rheology of the erythrocytes in the circulation, causing haemolytic anemia, vaso-occlusion, and vascular endothelial dysfunction and is characterized clinically by pain syndromes, anemia and its sequelae, organ failure including infection, and co-morbid conditions[1].Clinical

presentation of SCD in adults range from asymptomatic state to painful crisis, acute chest syndrome, aplastic crisis, haemolytic anaemia, jaundice, avascular necrosis of femoral head, hepatomegaly, splenomegaly, priaprism, leg ulcers, chronic renal failure, stroke, pulmonary hypertension, fetal loss, proliferative retinopathy[1].

According to WHO(World Health Organisation) 5% of world population suffer from hereditary hemoglobinopathies of which sickle cell hemoglobinopathy and thalassemia form the bulk (WHO fact sheet 2017)[2]. Sickle cell hemoglobinopathy is prevalent worldwide with frequency reaching very high proportion in certain African nations and in our country. This disorder is mostly prevalent in central Indian states of Maharastra, Gujarat, Madhya Pradesh, Chhatishgarh and Odisha. In our state most of cases of sickle cell hemoglobinopathy reside in western districts (prevalent ranging from 5% to 30%) although cases have been registered from all the districts. Both tribal and non-tribal populations suffer from this hemoglobinopathy.

With the advent of hydroxyurea therapy most of the acute manifestations like acute painful crisis and acute chest syndrome could be controlled giving rise to improved survivals. This has resulted in unfolding of chronic accumulative organ damage including that of kidney. Chronic kidney disease or chronic renal failure is now recognised as an important cause of mortality in patients of sickle cell disease.

Various renal manifestations in sickle cell disease include proteinuria, glomerulopathies, acute kidney injury and chronic kidney disease (CKD), impaired urinary concentrating ability, haematuria, increased risk of urinary tract infection and renal medullary carcinoma. All these manifestations can adversely affect the quality of life, increase health care cost, increased morbidity and mortality. CKD in SCD is associated with excess mortality at clinical baseline and during treatment with hydroxyurea. However the clinical picture is incomplete.Although in our institute a large number of sickle cell patients get hospitalized and attending sickle cell clinic, a systematic study of renal impairments in sickle cell disease has not been done.

This study was conducted to understand the different clinical types, pattern, and progression of renal impairment in patients of sickle cell disease. The information obtained will be utilised for early detection and intervention to prevent, treat and arrest the progression of renal impairment in SCD.

Aims and Objectives

GENERAL OBJECTIVES

To study the renal impairment in patients affected by sickle cell disease.

PRIMARY OBJECTIVES

1. To identify various types of renal impairment in SCD.
2. To record frequency and severity of renal impairment in SCD.
3. To record the decline in GFR over a period of time.

SECONDARY OBJECTIVES

1. To study the effect of hydroxyurea on renal impairment in SCD.
2. To identify factors if any that accelerates the progression of renal impairment during the study period.

II. Review Of Literature

RENAL MANIFESTATIONS IN SICKLE CELL DISEASE:

The fact that the kidney might be involved in sickle cell anaemia was recognized very early in 1910, by Herrick JB, who in his original reports mentioned the presence of urinary casts, leukocyturia, a slightly increased diuresis and urine of low specific gravity[3].

In 1923, Syndenstricker, Mulherin and Houseal first described macroscopic and microscopic studies of the kidney on necropsy[54] and after a gap of 25 years, reports of functional studies began to appear.

The kidney in SCD is affected by both the haemodynamic changes of a chronic anaemia and by the consequences of vaso-occlusion which are especially marked within the renal medulla. As a result, there are many abnormalities in renal structure and function (Sergeant, 1992)[55].

Various renal manifestations of sickle cell disease includes[56-70]:

1. Alterations in renal haemodynamics
(i) Increased renal blood flow rate
(ii) Increased renal plasma flow rate
(iii) Increased glomerular filteration rate
(iv) Decreased renal vascular resistance
(v) Decreased filtration fraction
(vi) Decreased medullary perfusion
2. Renal and glomerular enlargement
3. Hyperfunction of the proximal tubule
(i) Increased reabsorption of phosphate and β2-microglobulin
(ii) Increased secretion of creatinine and uric acid

(iii) Increased transport maximum of para-aminohippurate
4. Glomerulopathies
(i) Focal segmental glomerulosclerosis
(ii) Membranoproliferative glomerulonephritis
(iii) Thrombotic microangiopathy
5. Tubular deposits of iron
6. Chronic tubulointerstitial disease
7. Impaired function of the distal nephron
(i) Decreased urinary concentrating ability
(ii) Partial distal renal tubular acidosis
(iii) Impaired renal potassium excretion
8. Increased susceptibility to acute kidney injury
9. Chronic kidney disease and its progression to ESRD
10. Haematuria
11. Renal papillary necrosis
12. Increased susceptibility to urinary tract infection
13. Renal medullary carcinoma

RENAL FUNCTION ABNORMALITIES

Renal Haemodynamics:

Effects of age:

The changes in renal circulation are markedly influenced by age. Renal plasma flow (RPF) may be supranormal in children and young adults with SCD, decline to normal in third decade of life and become subnormal with increasing age (Ettledorf et al,1955)[80].

In children and young adults with SCD there are increases in effective renal blood flow (ERBF), effective renal plasma flow (ERPF), and glomerular filtration rate (GFR), although the filtration fraction is decreased (Hatch et al,1970)[81].

In patients with SCD over 40 years of age a marked decline in GFR and ERPF is common (Morgan and Sergeant,1981)[82] and progressive renal failure is a common cause of morbidity and mortality (Morgan et al,1987)[83]. But normal or above normal values may persist in some patients (Alleyne et al,1975)[57].

After age 25 to 30, the frequency of VOC tends to reduce and is replaced with signs and symptoms of chronic organ damage, including sickle cell nephropathy, heart failure, pulmonary hypertension and sickle hepatopathy (Sergeant GR,2013)[84].

Renal Concentrating Defect (Hyposthenuria):

Hyposthenuria (inability to concentrate urine under conditions of water deprivation) is a phenomenon that is almost universal in patients with SCD and also occurs in older people with sickle cell trait (de Jong & Statius van Eps,1985)[58]. This results in excess urination and nocturia. However urine volume does not exceed 2 to 3 litres per day. The normal diurnal variation in fluid and electrolyte excretion is lost (Addae and Konotey Ahulu,1977)[85].

It may be clinically apparent as enuresis and a tendency to dehydration under the age of 15 years. Adults with SCD can rarely achieve a urine osmolality greater than 450mOsm/kg following water restriction, and this impairment is vasopressin-resistant (de Jong PE etal,1985)[58]. This capacity for improvement is progressively lost with age, being almost negligible in subjects older than 15 years. The capacity to reabsorb sodium in the loop of Henle and distal tubule is intact in sickle cell anaemia (Hatch et al,1967)[86].

The defect in urinary concentration has important clinical implication because patients with SCD may develop sickle cell crisis (bone pain, anorexia, malaise) following moderate reduction in fluid intake. Crisis may develop in patients taking 1 litre of fluid daily for 3 days. Diuresis induced by cold may precipitate painful crisis. Thus as a general preventive measures dehydration and exposure to cold should be avoided in these patients.

Acid Base Homeostasis and renal Acidification:

Metabolic acidosis is not a feature of SCD and is not observed during sickle cell crisis, also the alkali therapy is not useful in the treatment and prevention of such crisis. Indeed, painful crisis have been provoked by making the patient acidotic by administration of ammonium chloride (Greenberg MS et al,1956)[91] or acetazolamide (Dos Santos WD et al,1959)[92]. In Jamaica in SS patients in the steady state, there is mild respiratory alkalosis, and when such patients have a painful crisis, there is no evidence of a metabolic acidosis (Ho Ping Kong H et al,1971)[93].

The ability to acidify urine following ingestion of ammonium chloride is decreased in adults with SS disease (Goosens et al,1967, Oster et al 1976)[96]. The defect was not corrected by phosphate loading although

normal acidification following infusion of sodium sulphate (Alleyne et al,1971)[57] suggesting abnormal tubular function. Ammonium excretion in SS disease appears normal.

Renal Handling of Potassium:

Hyperkalemia has not been reported to occur in sickle cell disease patients unless there is renal function impairment (Battle D et al,1982;De Fronzo RA et al,1979)[97,98] or stress such as volume contraction during a sickle cell crisis (Battle D et al,1982)[96]. Like the urine acidification defect, the defect in potassium secretion is not clinically apparent under normal conditions.

De Fronzo et al,1979, have demonstrated impaired potassium secretion in the presence of an intact renin-aldosterone axis, suggesting the presence of a primary defect in the renal tubular secretion of potassium[98]. It is probable that the abnormality in potassium metabolism could be due to the result of ischemic damage to the segment of distal nephron responsible for potassium excretion; however, the exact mechanism of decreased potassium excretion has not been elucidated. Despite impaired potassium secretion, the serum potassium level does not increase during potassium loading. This finding suggests an increased intracellular shift of potassium, probably caused by β2 adrenergic stimulation (Allon M et al,1990)[59].

Renal Handling of Phosphates and Urates:

Mild hyperphosphatemia associated with increased tubular reabsorption of phosphate has been observed in SCD patients with normal or elevated GFR. Increased RBC turnover leading to urate overproduction might be expected in SCD. Although urate over production begins early in life, hyperuricemia is rare in children with SCD. Nevertheless 30-40% of patients will develop hyperuricemia during their lifetime. Still reports of secondary gout are rare (Statius van Eps et al,1997;Allon M et al,1990)[59,56]. Jeffery D Lebensburger 2018, link the association and potential causal role for hyperuricemia on progression of SCA nephropathy[99].

Other Tubular Abnormalities:

In contrast to defective function of the distal tubules and collecting ducts, proximal tubular function is frequently greater than normal. An increased proximal tubular reabsorption of β2 microglobulin is found in patients with SCD (Allon M et al,1990)[56]. Renal sodium conservation appears adequate. Abnormally high fractional excretion of zinc has been reported in SCD leading to zinc deficiency which contributes to certain complications of SCD including growth retardation. Some investigators have suggested that enhanced proximal tubular activity might accompany the cortical hyperfiltration in SCD.

RENAL STRUCTURAL CHANGES

Renal size:

Renal size in SCD varies with age of the patients and the method of examination. Renal weight at autopsy was normal in young children (Alleyne et al,1975)[57], increased in older children and young adults and decreased in patients over 40 years (Morgan et al,1987)[83].

In children, bilateral renal enlargement was common in intravenous urography (Minkin et al,1997; Odita et al,1983)[100,101] and in adults, renal length exceeded 15cm in at least one kidney in about 10% Jamaicans (McCall et al,1987)[102] and Nigerians (Odita et al,1983)[101].

Renal structure:

Renal structure on imaging in SCD revealed that intravenous urography in 189 Jamaican adults showed mild cortical scarring, the frequency increasing from 8% in the 16-25 years old, to 45% in those over 35 years (McCall et al,1987)[102].

Calyceal abnormalities included calyceal cysts (6%), blunting (12%) and calyceal clubbing, which also increased with age from 28% in 16-25 years to 57% in over 35 years of age.

Radiological evidence of renal papillary necrosis occurred in 44 (26%) of adults patients in the Jamaican study (Pandya et al,1976;Odita et al,1983) [103,101]. Papillary necrosis has been observed as early as 4 ½ years of age (Harris et al,1976)[104].

Macroscopic appearance:

In young patients with normal renal function there is usually hypertrophy and smooth subcapsular surface. In older patients an increasing frequency of chronic kidney disease is associated with scarred, shrunken kidneys ranging from coarsely granular surface to gross distortion and scarring. The decreasing renal weight common in older patients is generally associated with cortical thinning.

Glomerular changes:

Enlarged glomeruli have been noted at autopsy and on biopsy (Pitcock et al,1970)[105]. Glomerular size increases with age. Increased size is not confined to juxta medullary glomeruli. Elfenbein et al (1974) noted glomerular hypertrophy throughout the cortex[106].The density of glomeruli tends to fall with age but the total glomerular area per unit area of cortex is significantly increased in SCD compared to controls.

On histologic examination the enlarged glomeruli are markedly hypercellular with lobulation of glomerular tuft and glomerular changes indistinguishable from those of proliferative glomerulonephritis (Pitcock et al,1970; Walker et al,1971)[105]. Reduplication of the basement membrane and mesangial proliferation may occur. There is progressive fibrosis of glomeruli which may be partial or complete.

Electron microscopy of glomeruli in SS disease without clinical renal involvement revealed occasional effacement of foot processes and local thickening of basement membrane (Pitcock et al,1970)[105]. These changes have been more marked in cases of SCD associated with nephrotic syndrome (McCoy et al,1969; Elfenbein et al 1974)[107,106].

Medullay changes:

The vascular disorganisation of the medulla results in tubular changes with atrophy, dilation, and proteinaceous casts. Round cell infiltrations and focal scarring are also common. Iron deposits occur in the cortical proximal convoluted tubule and glomeruli (Bernstein & Whitten,1960; Pitcock et al,1970) and may be related to degeneration of the tubular epithelium (Miller et al,1964)[108,109,105].

CLINICAL COURSE OF SICKLE CELL NEPHROPATHY

Clinical manifestations of sickle cell nephropathy include hematuria, proteinuria and the nephrotic syndrome, urine concentrating defects, renal insufficiency and hypertension.

Hematuria:

This is the most dramatic of the renal manifestations of sickle hemoglobinopathy. Massive hematuria associated with sickle cell anemia was first reported by Abel and Brown[110], but it was a report of seven similar cases by Goodwin, Alston and Semans[111] which first emphasized the significance of this as more than a chance association. Since that time hematuria has been reported in sickle cell trait, sickle thalassemia, sickle hemoglobin C and other combinations of hemoglobin S with abnormal hemoglobins. Lucas and Bullock[112] reviewed 124 cases of hematuria in sickle cell disease. The typical patient was a young man with painless, gross hematuria following mild trauma to the renal area. Bleeding occurred from the left side in 80% of cases and was bilateral in only 11%. A similar predilection for the left side has been noted[113,114] but others have found an equal incidence of bleeding from the two sides, and remarked that recurrences were usually on the ipsilateral side[115]. Due to its self-limiting nature, the management of haematuria is usually conservative and limited to good hydration, pain relief and antibiotics if necessary.

Renal stones, along with transitional cell carcinomas and renal clear cell carcinomas, may occur in the older patient group and must be excluded. One rare but devastating complication of both SCD and more commonly SCT is medullary carcinoma, a cancer specific to patients with sickle haemoglobinopathies.

Proteinuria and the nephrotic syndrome:

Proteinuria is the hallmark of glomerular injury in patients with sickle cell disease. Proteinuria is age-dependent in SCD. When assessed either as microalbuminuria (30–300 mg/g creatinine) or macroalbuminuria (>300 mg/g creatinine), and as comprehensively reviewed in 2014, [70] proteinuria occurs in up to 27% of patients in the first three decades,[70,118] and in up to 68% of older patients[70,74]. Nephrotic-range proteinuria occurs in 4% of patients with SCD and presages progressive CKD[119].

Glomerular involvement, one of the most prominent renal manifestations observed in SCD patients, is characterized by an early increase in glomerular filtration rate (GFR) associated with micro- or macroalbuminuria, followed by a gradual decline of GFR and chronic renal failure[120,66]. Aloni et al, reported the prevalence and determinants of microalbuminuria in children with SCD living in the Democratic Republic of Congo. In this cross-sectional study, microalbuminuria, defined on the basis of urine albumin/creatinine ratio (ACR), was detected in 18.5% of 150 children with homozygous SCD, in whom it ranged from 30 to 299mg/g[121]. Microalbuminuria, with or without hyperfiltration, is currently the earliest renal symptom reflecting probable glomerular injury detectable in adults and children with SCD[70]. The prevalence of albuminuria in SCD patients increases with age, from 4.5% to 26% in patients under the age of 21 years, to between 26% and 68% in older patients[74]. Guasch et al. found that 68% of 300 SCD adult patients had high rates of urinary albumin excretion, with 26% of these patients displaying macroalbuminuria[122]. In the cohort of 424 adult British patients of African origin studied by Day et al, microalbuminuria was detected in 28% of the patients aged 16-25 years, 38% of the patients aged 26-35 years and 50% of those aged 36-45 years[123].

Renal Insufficiency:

Renal insufficiency in SCA was defined as a creatinine clearance <90 ml/min using Crockcroft-Gault, (1976) equation. It was reported that 21% of patients with SCA had renal insufficiency while 27% of patients with other sickling disorders had renal insufficiency but the percentage of patients with renal insufficiency and advanced kidney failure(chronic kidney disease stage 3 or higher) was higher in SS disease than other sickling disorders(Guasch et al.,2006)[74]. Guasch et al.(1997)[124]. previously showed renal insufficiency in SCA results from a glomerulopathy, which can be detected by the presence of albumin and other large molecular weight proteins in urine. Increased albumin excretion rate (AER) occurs in approximately 70% of adults with haemoglobin SS disease and about 40% in adults with other sickling disorders.. Patients with SCD exhibit a rapid decline in eGFR over time. The decline in eGFR is associated with markers of disease severity and associated comorbid conditions (Vimal K. Derebail et al,2018)[126].

Hypertension:

Lower systolic and diastolic blood pressure have been found in steady state of patients with SCD. The typical age related increase in blood pressure are not observed. A recent survey by Johnson and Giorgo et al[127] found that the prevalence of hypertension to be significantly less in patients with SCD. The appearance of hypertension may be a marker of renal insufficiency in SCD. Power et al, 2002[128], noted that hypertension preceded the diagnosis of renal failure in patients with SCD in 36% of the patients. None of his patients without renal insufficiency had either hypertension or the nephrotic syndrome.

Renal Papillary Necrosis:

Papillary necrosis is associated with all of the SCDs as well as with sickle cell trait. The propensity for these individuals to develop papillary necrosis is thought to be related to obstruction of the microvasculature in the vasa rectae with resulting medullary ischemia and infarction. Papillary necrosis is typically associated with hematuria. In addition, sloughing of the renal papillae can occasionally produce obstruction to urine outflow and renal failure[59].

The functional and anatomic disruption associated with sickling in the blood vessels of the renal medulla plays a central role in the pathogenesis of renal papillary necrosis (RPN). The overall incidence of RPN in sickle cell hemoglobinopathy (SCH) evaluated by intravenous pyelography was 39%. RPN occurred in 56% in HbAS, 33% in HbSS, 65% with HbSC and 50% with HbS Thal. The age at the time of diagnosis was usually under 40 years.

RPN may appear as acute kidney injury, rapidly evolving septicaemia, gross haematuria or urinary tract infection. It may be completely asymptomatic. Painless gross haematuria is the most common symptom, renal colic secondary to the passage of blood clot or sloughed papillae is rare. Asymptomatic microscopic haematuria is the most common clinical manifestation.

Acute kidney injury:

AKI occurs in 4–10% of hospitalized patients with SCD, and is more frequent in patients with acute chest syndrome (13.6%) than in patients with painful crisis (2.3%)[130,131]. AKI is prognostically important in SCD, as it predicts a less favourable outcome among patients who are transferred to the intensive care unit[132]. AKI develops in some 75% of episodes of painful crisis that are complicated by acute multiorgan failure; haemodialysis is needed during 18% of these episodes[133]. In prospectively studied patients, a reversible 15% reduction in creatinine clearance occurs during painful crisis[134]. Factors that predispose to AKI include volume depletion, rhabdomyolysis, infections, and the use of nonsteroidal analgaesics[56-61].

Chronic Kidney Disease:

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for more than three months, with implications for health (KDIGO 2012). It is more common in people with HbSS and HbSβ0 than in people with HbSC or HbSβ+; however, there is conflicting evidence relating to the relative prevalence of CKD in different SCD genotypes (Nath 2015, Yee 2011)[120,136]. The prevalence of CKD increases with age, affecting over 50% of people with SCD who are over 40 years of age (Gosmanova 2014)[137].

The risk of end-stage renal disease (ESRD), defined as requiring long-term dialysis or transplantation, is around 12% (Powars 2005)[138]. Risk factors for ESRD include proteinuria, anaemia, hypertension, and HbSS genotype (Ataga 2014)[70].

Effect of ACE inhibitor and Hydroxyurea:

Angiotensin-converting-enzyme inhibitors are employed to reduce proteinuria and delay the progression of CKD in patients with SCD[125]. Although this approach has not been vigorously tested in patients with SCD[139]. It is recommended on the basis of the general efficacy of these agents in CKD. Recommendations made by an expert panel in 2014 include the initiation of treatment with these agents in patients with

microalbuminuria and macroalbuminuria, even when blood pressure is normal [140]. Interest also surrounds the use of hydroxyurea, as such treatment diminishes renal enlargement and improves urinary concentrating ability in infants[141] decreases glomerular hyperfiltration in children[142] and is associated with less albuminuria in adults[143].

Renal Replacement Therapy:

Both maintenance hemodialysis and renal transplantation have been shown to be viable options for patients with sickle cell nephropathy who progress to ESRD. Survival of patients on hemodialysis has been shown to be equivalent to other nondiabetic ESRD patients[144]. Renal transplantation is used less frequently, possibly reflecting the limited experience with renal transplantation in this patient population.

Studies specifically pertaining to ESRD secondary to SCN are few. Powars et al (1991)[128], reported that ESRD heralded a very poor prognosis, as not only was the average age at diagnosis very young (23.1 years in those with HbSS and 49.9 years in those with HbSC) but the mean time to death after reaching ESRD was only 4 years despite being on haemodialysis. A similar finding was reported by Saxena et al (2004a)[145] who retrospectively compared a group of 11 patients with SCD in Saudi Arabia to 192 patients with renal failure of other causes. Those with SCD suffered more infectious complications, and lived on average, for only 27 months after commencing RRT and were significantly younger when they died (31 years verses 47.8 years).

III. Materials And Methods

PLACE OF STUDY:

Department of General Medicine (both indoor and outdoor) and Sickle Cell Clinic and molecular biology laboratory, Veer Surendra Sai Institute of Medical Science and Research, Burla.

STUDY SUBJECTS:

The study was conducted amongst adult patients suffering from sickle cell disease, both homozygous and compound heterozygotes with features of renal impairment.

STUDY PERIOD:

November 2017 to October 2019.

STUDY TYPE:

Hospital based longitudinal observational study.

SAMPLE SIZE:

During the study 50 adult sickle cell disease patients with features of renal impairment were enrolled in our study.

SELECTION OF CASES:

Sickle cell disease cases previously diagnosed by sickling test, Hemoglobin electrophoresis and high performance liquid chromatography(HPLC) who presented with features of renal impairment were considered in the study. The patients diagnosed to have sickle cell disease meeting the inclusion and exclusion criteria as mentioned below were enrolled in the study only after getting informed consent from them (format of consent form enclosed).

INCLUSION CRITERIA:

Adults patients with age 15 years or more diagnosed with sickle cell disease both homozygous and compound heterozygous states with features of renal impairment based on abnormal findings of specific parameters of renal impairment like 24 hours urine protein, blood urea, serum creatinine, eGFR, abdominal ultrasonography.

EXCLUSION CRITERIA:

a) Patients having kidney disease other than from sickle cell disease.
b) Patients not giving consent.
c) Patients suffering from sepsis, diarrhea, shock from causes other than sickle cell disease.
d) Patients with malaria, leptospira, scrub typhus and other infectious disease which presents with renal failure.
e) Patients of sickle cell disease with diabetes mellitus and long standing hypertension.

SUBJECT ANALYSIS

All patients were examined clinically with records of patient particulars and clinical parameters mentioned below in a prescribed format.

- Age, sex, body weight, height, chief complaints, history of present illness, personel history, family history, previous treatment history.
- Thorough general and systemic examination.

LABORATORY INVESTIGATIONS

Diagnosis of sickle cell disease is done by patients having a positive sickle slide test, Hemoglobin electrophoresis showin S and SF bands are diagnosed to have sickle cell disease who have not been transfused blood in the last 3 months. Further stratification of SCD types were done by detection of various Hb fraction in HPLC and mentioned later.

(i) SICKLING TEST:

The test used in present study is as described below:

A drop of capillary blood was obtained by finger prick and taken over a clean glass slide. A cover slip was put over it and carefully sealed with molten wax, so that no air bubble remains inside. This preparation was kept in room temperature for 24 hours and then examined under microscope to detect presence of sickle erythrocytes

(ii) HEMOGLOBIN ELECTROPHORESIS (Systronics India 606H):

Although the sickling test and haemoglobin solubility test detect the presence of HbS, haemoglobin electrophoresis is mandatory for precise diagnosis of sickle cell hemoglobinopathies.

The principles of Hb electrophoresis at alkaline pH are based on the haemoglobin molecule, which follows certain amino acid substitution. In practice the method requires a source of current, a buffer system and a supporting medium. Of the media used Agarose gel was used as a media for the purpose keeping in view its consistent performance in Odisha sickle cell project and it is also less expensive.

(iii) HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC):
(BIO-RAD VARIANT II)

High performance liquid chromatography (HPLC), is a relatively fast and reproducible method, and therefore used for the determination of various haemoglobin fractions, including HbA2 and HbF, HbS, HbC, HbD, HbE etc.

It can be used to separate and determine area under curve as percentages for HbA2 and HbF and to provide qualitative determinations of abnormal haemoglobin.

Principle: It is a cation exchange high performance liquid chromatography. Hemolyzed specimens are maintained at $12 \pm 2^{o}C$ in the automatic sample chamber. Specimens are sequencially injected into the analysis stream at 6.5 minutes intervals for a throughput of 9 samples per hour.

Two dual-piston pumps and pre-programmed gradient control the elution buffer mixture passing through the analytical catridge. The ionic strength of the elution buffer mixture is increased by raising the percent contribution of elution buffer 2. As the ionic strength of the mixture increases more strong retained haemoglobin elute form the analytical catridge.

A dual-wavelength filter photometer (415 and 690 nm) monitors the haemoglobin elution from the catridge, detecting absorbance changes at 415 nm. Analysis of data from the detector is processed by the built-in integrator and printed on the sample report. At the end of each sample analysis, a copy of the chromatogram and report data is automatically generated.

Other laboratory Investigations:

Hematological Parameters:

Complete blood count (CBC) with facility to measure Hb Level, total leukocyte counts, haematocrit and platelet count were obtained during the first visit in an automated blood counter (Sysmex, KX-21), in sickle cell institute, VIMSAR, Burla.

Biochemical Parameters:

The following biochemical parameters were obtained at Regional Diagnostic Centre (RDC), VIMSAR, Burla with Cobas c311 automated counter Liver function test: To measure serum total and direct bilirubin, aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP). Fasting plasma glucose, blood urea and serum creatinine, serum albumin, serum uric acid, serum Na^{+}, K^{+} and Ca^{++}. Serum LDH value was obtained by Vitro 250 automated counter.

Urine examination:

Hematuria was detected by Benzedene test and presence of red cell on routine microscopy of urine. Leukocyturia was detected by presence of pus cells on urine microscopy. Proteinuria was detected in these patients by using a dip stick test. A 24 hour urine specimen was collected from patients to measure the total protein excretion. Urine microalbumine estimation was done by nephelometry method. Patients who had proteinuria (Urine protein excretion of 150 mg per day) were subjected to estimation of eGFR.

Estimation of Glomerular Filteration Rate (GFR):

Estimated glomerular filtration rate (eGFR) was obtained using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation 2009, as mentioned below:

$GFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa,1)^{-1.209} \times 0.993^{Age}$
Multiply by 1.018 for women
Multiply by 1.159 for African ancestry
Where S_{Cr} is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of S_{Cr}/κ or 1,and max indicates the maximum of S_{Cr}/κ or 1. (Harrison's principle of internal medicine 20th edition pg 2112-2113).

Imaging study of kidney:

Ultrasonography of abdomen and pelvis (KUB) was done at the Department of Radiology after preparing the patient prior to investigation. The size of the kidney, cortical echogenicity and corticomedullary differentiation were noted down.

Follow up of renal function deterioration:

The patients enrolled in the study were followed up at 4 months intervals. In each visit, blood urea and serum creatinine were measured and the eGFR was calculated. The values obtained were analysed for noting down the progression of chronic kidney disease.

Data Analysis:

Data were collected systematically entered in study proforma and subsequently transferred to Microsoft excel sheet 2016 and and observations were shown in the form of graphs, pie chart and line diagrams using MS excel sheet 2016. Statistical analysis was done using Graphpad prism version 8.

IV. Observations and Results

Fifty patients diagnosed as sickle cell disease with features of renal impairment who satisfied the selection criteria were included in the study. These patients were followed up in 4 months intervals for a period of 24 months to look for the progress in renal impairment with serial eGFR measurement. Various observations made are depicted below in the form tables and figures with description.

TABLE-1: District Wise Distribution of Sickle Cell Disease Patients with Renal Impairment (N=50) in Different Districts of Odisha State

DISTRICT	NO. OF CASES	PERCENTAGE OF CASES
ANGUL	2	4%
BARGARH	20	40%
BALANGIR	7	14%
BOUDH	2	4%
JHARSUGUDA	4	8%
KALAHANDI	4	8%
NUAPADA	1	2%
SAMBALPUR	8	16%
SONEPUR	1	2%
SUNDERGARH	1	2%

From the above table it was seen that most of the cases were from districts Bargarh followed by Sambalpur and Balangir of Odisha state, India.

Figure -1: District Wise Distribution of SCD Patients with Renal Impairment

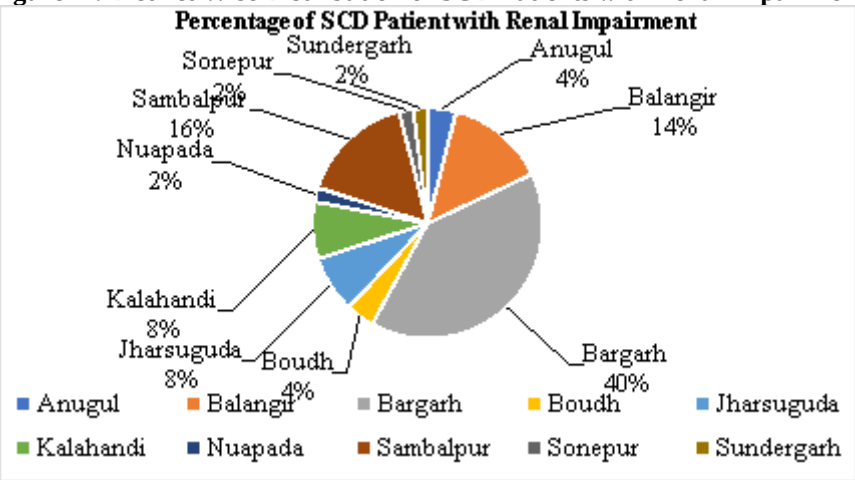


TABLE – 2: Age and Sex Distribution of SCD Patients with Renal Impairment between 15-65 Years (N=50)

	CASES		
Age group(in years)	**MALE (Percentage)**	**FEMALE (Percentage)**	**Total (Percentage)**
15-25	6(12%)	2(4%)	8(16%)
26-35	14(28%)	2(4%)	16(32%)
36-45	10(20%)	6(12%)	16(32%)
46-55	6(12%)	4(8%)	10(20%)
56-65	-	-	
Total	36(72%)	14(28%)	

The total number of cases was 50. Out of which male and female were 36 (72%) and 14 (28%) respectively. From the table it is observed that majority of patients were in the age group 26-35 and 36-45 years together accounting for 64% of cases. Age and Sex wise difference exists from the above observation with maximum number of males and females in the age group of 26-35 yrs and 36-45 yrs respectively. No patients were found in the age group of 56-65 years.

FIGURE-2: Age and Sex Distribution of Cases

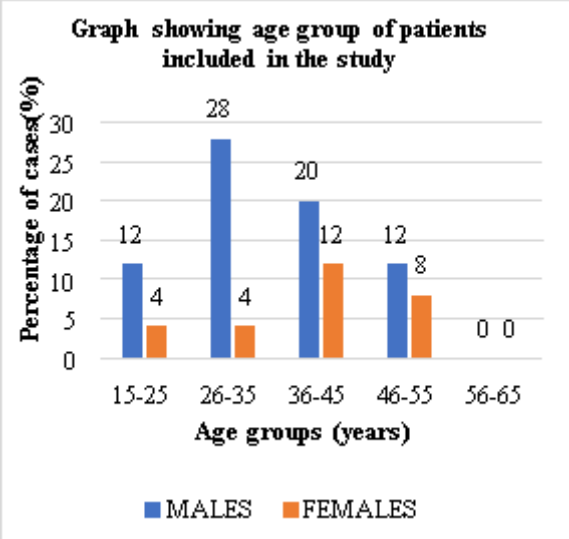


TABLE-3: Mean Age of SCD Patients with Renal Impairment (N=50)

Sex	CASES		
	Number of cases(n)	(Mean age in years ± SD)	Median age
Male	36	(35.05±9.43)	33.5
Female	14	(39.07±12.00)	41
Total	50	(36.18±10.25)	36

The mean age of male and female of SCD with renal impairment was found to be 35.05±9.43 years and 39.07±12.00 years respectively and the median age of male and female was 33.5 and 41 years. Males presented with renal impairment at an earlier age compared to females. The average age of cases was found to be 36.18±10.25 years.

FIGURE-3: Bar diagrams showing mean age of both sex

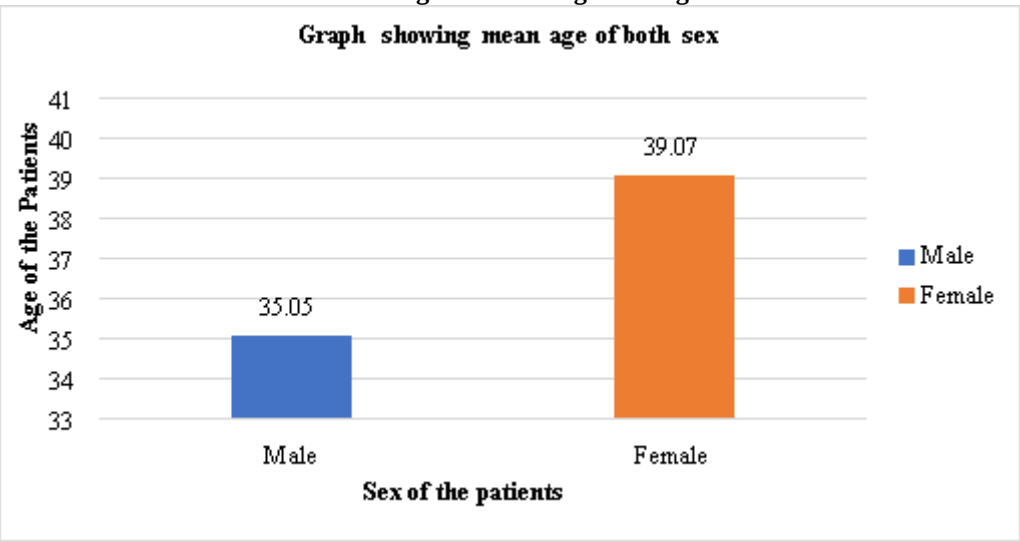


TABLE – 4: Caste Distribution among Patients of SCD with Renal Impairment (N=50)

Caste	No. of Patients	Percentage (%)
Kulta	17	34%
Scheduled Caste	13	26%
Gouda	8	16%
Scheduled Tribe	4	8%
Agharia	3	6%
Bhulia	3	6%
Chasa	2	4%

Table - 4 shows the distribution of caste within the sickle cell disease patients with renal impairment enrolled in the study. It was found that it is more common in Kulta caste, with a incidence of 34% followed by 26% in Scheduled caste and then to 16% in Gouda community in western part of Odisha, seen in our study.

FIGURE-4: Bar diagrams showing distribution of cases among different caste

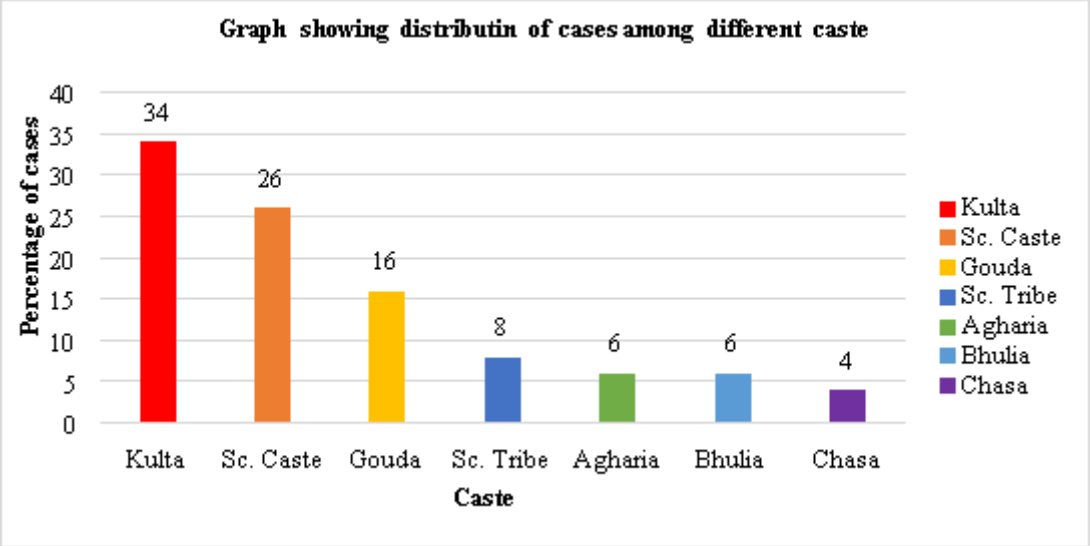


TABLE- 5: Clinical Manifestations of SCD Patients with Features of Renal Impairment (N=50)

Clinical manifestations	No. of cases	Percentage (%)
VOC	35	70%
Fever	12	24%
Pallor	46	92%
Jaundice	23	46%
Puffiness of face	21	42%
Pedal edema	14	28%
Ascites	5	10%
Nausea	4	8%
Vomiting	5	10%
Polyuria	12	24%
Oligura	5	10%
Anuria	0	0

Table - 5 shows different clinical presentation of sickle cell disease with renal impairment. The most common presenting features were pallor (92%), followed by vaso-occlusive crisis (70%) and then jaundice (46%). Polyuria (24 hr urine output more than 3000ml) being a mode of presentation in24% cases.

FIGURE – 5: Bar diagrams showing clinical manifestations of cases

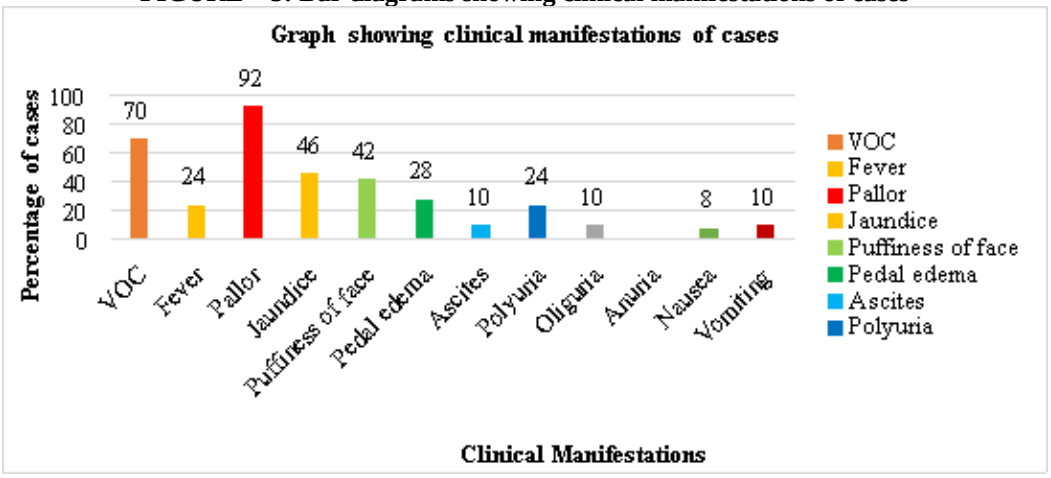


TABLE- 6: Hepatosplenomegaly in SCD with Renal Impairment

Palpation of Liver and Spleen	SCD with renal impairment	
	No. of cases	Percentage (%)
Hepatomegaly	16	32%
Splenomegaly	29	58%
Hepatosplenomegaly	11	22%

Table - 6 shows the incidence of hepatosplenomegaly in patients of SCD with features of renal impairment. 32% of cases presented with hepatomegaly, 58% cases presented with splenomegaly whereas 22% of cases presented with hepatosplenomegaly.

FIGURE – 6: Bar diagrams showing percentage of cases with hepatosplenomegaly in patients of SCD with renal impairment

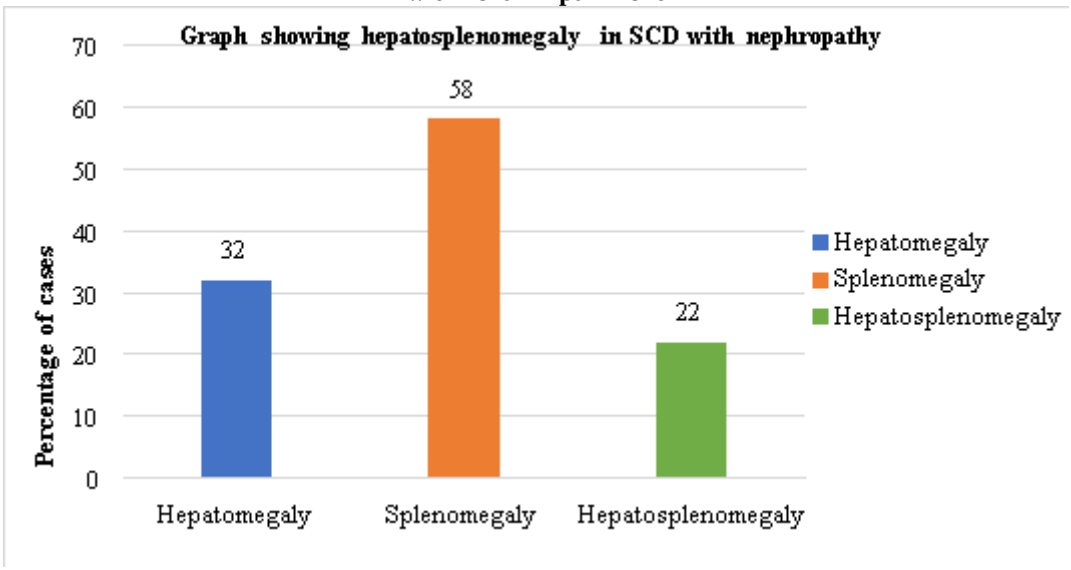


TABLE-7: Haemoglobin Level in SCD with Renal Impairment (N=50)

Hb level (gm/dL)	Cases	
	No. of patients	Percentage (%)
<6	29	58%
6 – 10	19	38%
10 – 12	2	4%
>12	-	-
Mean±SD	6.07±1.58 gm/dL	

Table -7 shows the haemoglobin levels in patients SCD with renal impairment. In maximum no. of cases (58%) the haemoglobin concentration was < 6gm/dL. The mean haemoglobin level was found to be 6.07 gm/dL.

TABLE-8: Hematocrit (HCT), Total Leukocyte Count (TLC), Total Platelet Count (PLT) in SCD Patients with Renal Impairment (N=50)

Blood Parameters	Range (min-max)	Mean ± SD
Hematocrit (%)	8.3 – 30.6	17.84 ± 5.59
TLC(x 10^3/cmm)	8.3 – 30.6	10.97 ± 8.47
PLT(x 10^3/cmm)	32 - 377	207.9 ± 91.53

Table - 8 shows that the mean values of haematocrit was 17.84 %, that of total leukocyte count was 10.97 ($x10^3/mm^3$) and for platelet the mean value was 207.9 ($x10^3/mm^3$) among the cases of sickle cell disease with renal impairment included in the study.

Two of the patients had sickle cell hepatopathy with very high bilirubin and hepatic enzymes who were not considered in calculation of mean.

TABLE – 9: Liver Function Test in Patients of SCD with Renal Impairment (N=50)

LFT	Range (min-max)	Mean ± SD
Total Bilirubin (mg/dl)	0.3-9.93	2.24 ± 2.47
Direct Bilirubin (mg/dl)	0.1-3.22	0.77 ± 0.89
Indirect Bilirubin (mg/dl)	0.11-6.71	1.42 ± 1.65
Aspartate Transaminase(IU/L)	5-150	45.8± 33.32
Alanine Transaminase(IU/L)	6-100	28.2 ± 18.84
Alkaline Phosphatase(IU/L)	66-364	137.94±82.53

Table - 9 shows the mean values of different LFT parameters in patients of SCD with features of renal impairment. The mean value for total bilirubin, direct bilirubin and indirect bilirubin was 2.24 mg/dl, 0.77 mg/l and 1.42 mg/dl respectively. The mean values of AST, ALT and ALT in our study was found to be 45.8 IU/L , 28.2 IU/L and 137.94 IU/L respectively.

TABLE – 10: Fasting Blood Glucose, Serum Albumin, Serum Uric Acid in Patients of SCD with Renal Impairment (N=50)

	Range (min-max)	**Mean ± SD**
Fasting blood glucose(mg/dl)	71-102	85.92 ± 7.77
Serum Albumin(gm/dl)	1.9-4.1	3.26 ± 0.59
Serum Uric acid(mg/dl)	4.8-12	7.79 ± 1.73

Table -10 shows the mean level of fasting blood glucose, serum albumin, and serum uric acid in patients of SCD with renal impairment.The mean FBS, serum albumin and serum uric acid was found to be 85.92 mg/dl, 3.26 gm/dl and 7.79 mg/dl respectively

TABLE – 11: Incidence of Hypertension in Patients of SCD with Renal Impairment (N=50)

Blood pressure (mm of Hg)	**No. of patients**	**Percentage (%)**
< 120/80	42	84%
120-139/80-89	3	6%
140-159/90-99	5	10%
SBP (Mean ± SD)	113.88 ± 16.41	
DBP (Mean ± SD)	72.56 ± 9.52	

Table - 11 shows incidence of hypertension in SCD disease patients with renal impairments.In the study 6% of patients were prehypertension stage (120-139/80-89), 10% of cases were under stage 1(140-159/90-99) while 84% of patients were normotensive with a BP of <120/80 mm Hg.The mean Systolic and Diastolic blood pressures were 113.88 and 72.56 mm of Hg respectively.

TABLE-12: Serum Electrolytes in SCD Patients with Renal Impairment (N=50)

Electrolytes (mmol/L)	**Cases**		
	Range (mmol/L)	**No. of case**	**percentage**
Serum potassium(K^+)	3.5 – 5.5	40	80%
	<3.5	7	14%
	>5.5	3	6%
Serum potassium (K^+) (Mean±SD)	4.05 ± 0.81		
Serum sodium (Na^+) (Mean±SD)	135.34 ± 4.04		
Serum ionized Ca^{++} (Mean±SD)	0.95 ± 0.10		

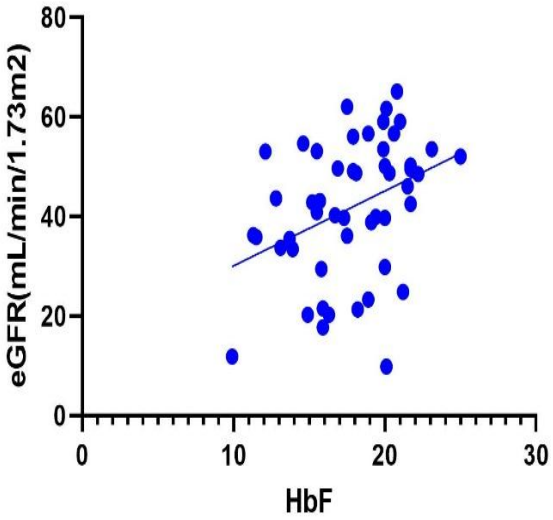
Table - 12 shows that among SCD patients with renal impairment 80% of patients are normokalemic, with 14% are hypokalemic and 6% of patients are hyperkalemic.The mean levels of Serum Na^+, K^+ and Ca^{++} of patients are 135.34, 4.05, and 0.95 mmol/dL respective

TABLE-13: Electrophoresis in Patients of SCD (SS) with Renal Impairment (N=50)

Hemoglobin Electrophoresis	**Mean ± SD**
HbA0	2.00 ± 0.84
HbA2	2.88 ± 0.77
HbS	69.8 ± 11.08
HbF	17.76 ± 4.20

All patients taken in this study were homozygous for sickle cell disease (SS).Table -13 shows the haemoglobin electrophoresis pattern in the study group of SCD with renal impairment.The mean level of HbA0, HbA2, HbS and HbF in our study was found to be 2.0, 2.88, 69.8 and 17.76% respectively. Although HbA0 window shows mean of 2.0, it does not reflect presence of HbA (adult haemoglobin) and is due to elution of unknown Hb variants of HbA0 window.

FIGURE - 7



The above Scatter diagram showed the correlation between the fetal haemoglobin level and eGFR value with Pearson coefficient r being 0.3671 and P value of 0.009 which is found to be statistically significant.

TABLE – 14: Abnormal Urinary Findings in Patients of SCD with Renal Impairment (N=50)

Urine parameters			Cases	
			Number	Percentage (%)
Proteinuria >150 mg/24 hour urination			50	100%
Haematuria > 1 RBC in centrifused urine			5	10%
Pyuria > 5 pus cell/hpf in centrifused urine			12	24%
Cast	Granular	2	6	12%
	Waxy	4		

Table -14 shows abnormal urinary findings in SCD patients with features of renal impairment.Among the cases included in the study 100% of patients have proteinuria with a urine protein excretion of >150mg/24 hours, 10% patients have haematuria with 24% of cases having pyuria and 12% patients have cast in their urine.

TABLE-15:24 Hours Urine Protein in Patients of SCD with Renal Impairment (N=50)

24 hour urine protein (mg/day)	Cases	
	No. of patients	Percentage (%)
< 150	-	-
150 – 500	31	62%
5000-1000	10	20%
1000-2000	4	8%
2000-3000	2	4%
> 3000	3	6%

Table-15 shows percentage of SCD patients with renal impairment manifesting different ranges of proteinuria. In our study 31(62%) patients having proteinuria in range of 150-500 mg/day, 20% had 500-1000 mg/day, 8% had 1000-2000 mg/day, 4% had 2000-3000 mg/day and 6% had in nephrotic range proteinuria.

FIGURE – 8: Bar diagrams showing percentage SCD patients with renal impairment with different range of proteinuria expressed in mg/day.

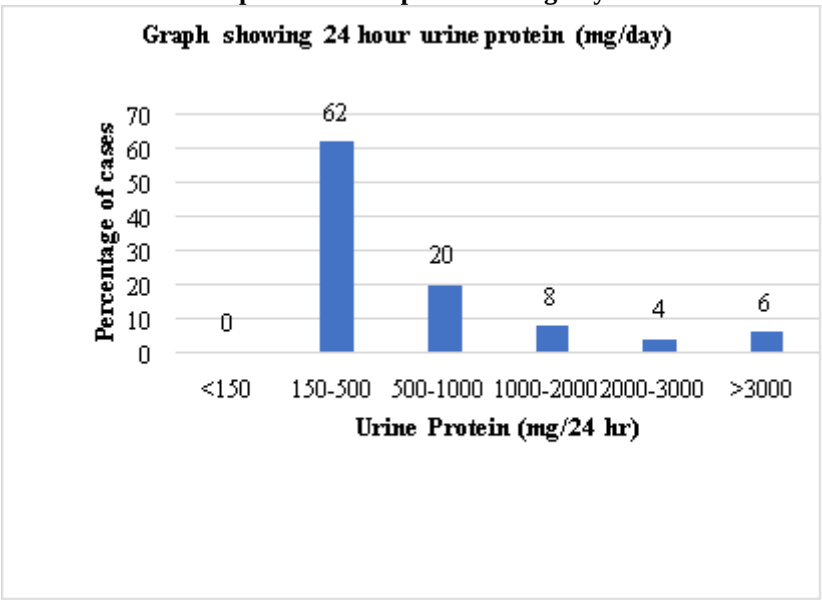


TABLE – 16: Microalbuminuria in SCD Patients with Renal Impairment (N=50)

Microalbuminuria (mg/g creatinine)	No of cases	Percentage (%)
< 30 mg/g	5	10%
30-300 mg/g	37	74%
>300 mg/g	8	16%

Table -16 shows the different grades of microalbuminuria in patients of SCD with renal impairment. In our study it was seen that microalbuminuria (30-300mg/g) was detected in 37 (74%) of patients while macroalbuminuria (>300mg/g) was seen in 8 (16%) of patients.

FIGURE – 9: Bar diagrams showing percentage distribution among cases with different grades of microalbuminuria in mg/g of creatinine.

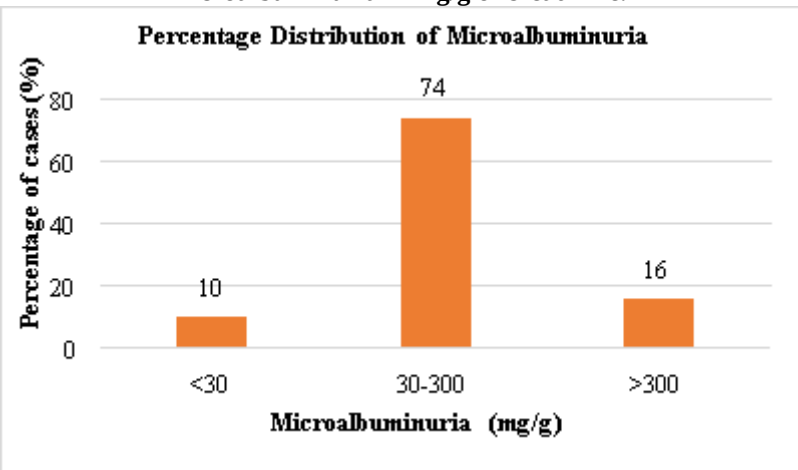


TABLE – 17: Blood Urea in SCD Patients with Renal Impairment over a Period of Time (N=50)

Time period (months)	Blood Urea level (mg/dL) Mean ± SD
0 month	47.6 ± 15.89
4 month	73.82 ± 49.71
8 month	69.78 ± 32.98
12 month	74.36 ± 44.06
16 month	80.14 ± 44.88
20 month	85.26 ± 58.36
24 month	85.84 ± 33.36

Table - 17 shows the mean levels of blood urea in patients of SCD with renal impairment.The mean blood urea level on start of study and followup in intervals of 4 months were found to be 47.6, 73.82, 69.78, 74.36, 80.14, 85.26 and 85.84 mg/dL respectively.

FIGURE – 10: Graph showing a line diagram of mean Blood Urea level over a period of time (solid blue) and the trend line (dotted red)

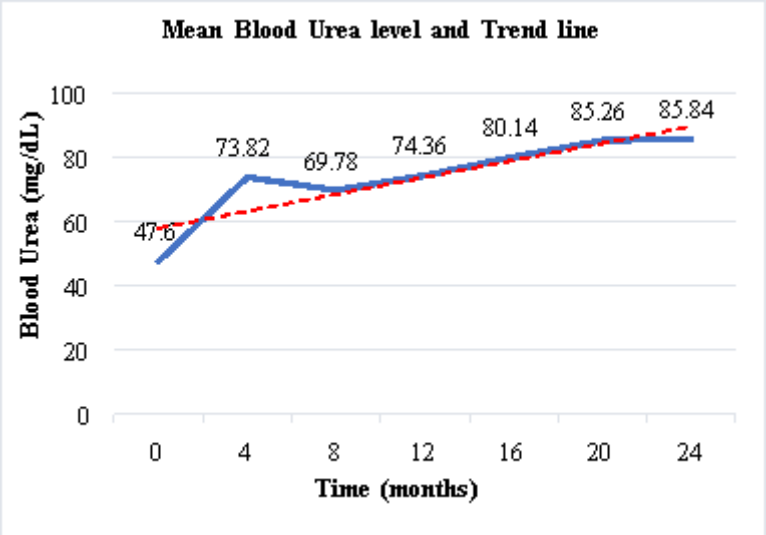


TABLE – 18: Serum Creatinine in SCD Patients with Renal Impairment over a Period of Time (N=50)

Time Period in months	Serum Creatinine (mg/dL) Mean ± SD
0 month	2.10 ± 0.93
4 month	2.59 ± 1.89
8 month	2.65 ± 1.7
12 month	2.87 ± 1.99
16 month	2.92 ± 1.90
20 month	3.07 ± 2.06
24 month	3.09 ± 2.01

Table - 18 shows the mean levels of Serum Creatinine in patients of SCD with renal impairment. The mean serum creatinine level on start of study and followup in intervals of 4 months was found to be 2.12, 2.59, 2.65, 2.87, 2.92, 3.07, and 3.09 mg/dL respectively.

FIGURE-11: Graph showing line diagram of mean serum creatinine level over a period of time (solid green) and the trend line (dotted blue).

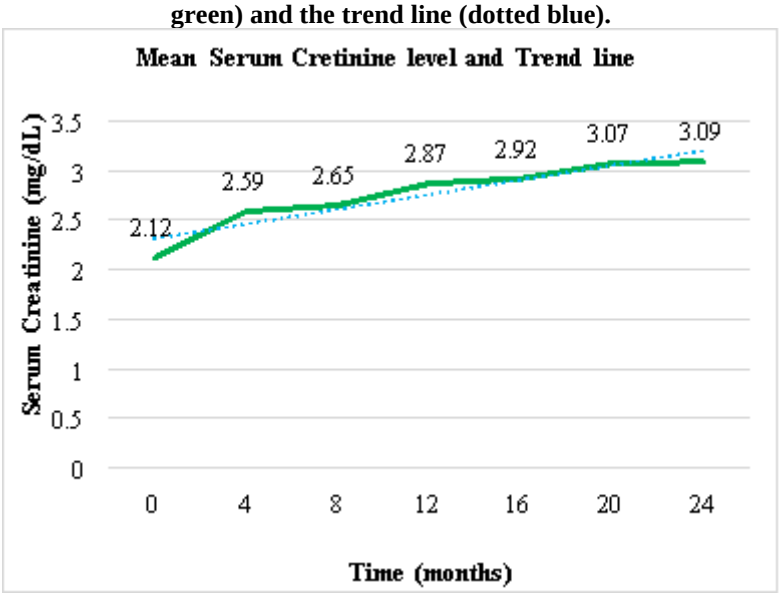


TABLE – 19: eGFR in patients of Sickle Cell Disease with Renal Impairment (N=50)

Time Period in months	eGFR (mL/min/1.73m^2)Mean ± SD	Grade as per mean value
0 month	41.75 ± 13.81	G3b
4 month	40.63 ± 18.72	G3b
8 month	38.42 ± 19.49	G3b
12 month	36.12 ± 18.19	G3b
16 month	34.46 ± 16.61	G3b
20 month	32.60 ± 15.92	G3b
24 month	31.06 ± 14.30	G3b

Table - 19 shows the mean levels of eGFR in patients of SCD with renal impairment. The mean eGFR level on start of study and followup in intervals of 4 months was found to be 41.75, 40.63, 38.42, 36.12, 34.46, 32.60, and 31.06 ml/min/1.73m^2 respectively. All patients were under Grade 3b of CKD as per KDIGO 2012.

FIGURE – 12: Graph showing line diagram of mean eGFR level over a period of time (solid red) and the trend line (dotted black).

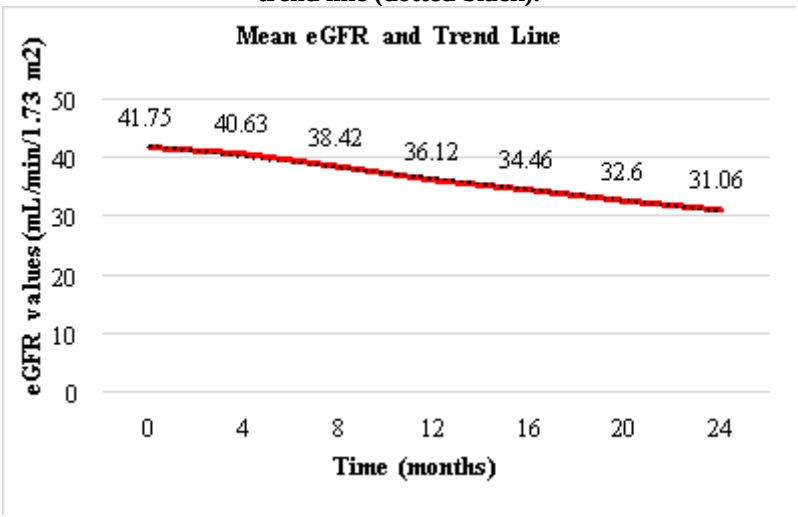


TABLE – 20: Ultrasonogram of KUB in SCD Patients with Renal Impairment (N=50)

USG Parameters		No. of cases	Percentage (%)
Kidney Size	Normal	40	80%
	Decreased	8	16%
	Increased	-	-
CMD*	Intact	36	72%
	Diminished	14	28%
Cortical Echo**	Normal	28	56%
	Increased	22	44%

CMD*- Cortico-medullary differentiation Echo**- Echogeneicity

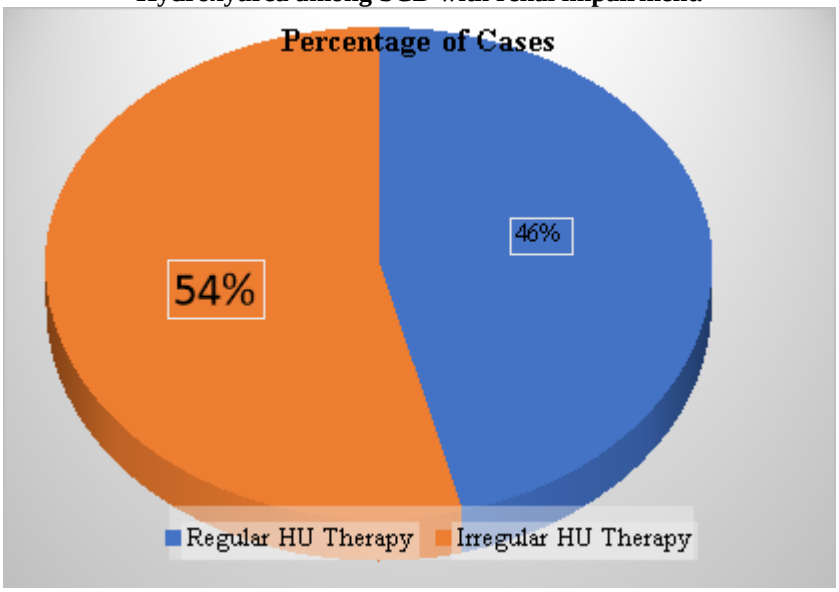
Table - 20 shows the ultrasonogram findings of kidneys in patients of SCD with features of renal impairment. It was found that 80% of cases have a normal kidney size whereas 16% have a decrease in their kidney size. Cortico-medullary differentiation (CMD) was lost in 72% of cases and Cortical ECHO was increased in 44%.

TABLE – 21: Hydroxyurea Therapy in SCD Patients with Renal Impairment (N=50)

Therapy with Hydroxyurea **(HU)**	Cases	
	No.of cases	**Percentage (%)**
Regular HU therapy	23	46%
Irregular HU therapy	27	54%

Table - 21 shows percentage of patients of SCD with renal impairment with regular and irregular Hydroxyurea therapy. It was found that 23 patients (46%) were on a regular hydroxyurea therapy and 27 patients (54%) were on irregular hydroxyurea treatment. All patients were on hydroxyurea therapy as once registered in sickle cell clinic HU therapy is started as per recent guideline [Expert panel recommendation 2014].

FIGURE-13: Pie chart showing percentage of cases on regular and irregular treatment with Hydroxyurea among SCD with renal impairment.



V. Discussion

In the present study held during the period November 2017 to October 2019, carried out in the Department of Medicine and Sickle cell clinic, VSSIMSAR, Burla, 50 patients with renal impairment were studied. All patients were confirmed to be having homozygous Sickle cell disease by Hb electrophoresis and HPLC.

In the present study it was seen that maximum number of cases of SCD with renal impairment were from Bargarh district followed by Sambalpur and Balangir in the state of Odisha. (Table -1, Fig - 1)Out of the 50 cases of SCD who presented to us with features of renal impairment males and females accounted for 72% and 28% of cases respectively (Table - 2, Fig - 2). Although there is no gender predilection for renal failure in most series, Nissenson and Port 1989, analyzed and reported a male predominance of sickle cell nephropathy patients in U.S[144].

Majority of patients in the present study fall in the age group of 26-35 years and 36-45 years, together accounting for 64% of cases (Table - 2, Fig - 2). Sergeant GR (2013) in his study reported that after age 25 to 30 years, the signs and symptoms of chronic organ damage like Sickle cell nephropathy tends to increase[84].

The mean age of patients of SCD with renal impairment in our study was 36.18 years (Table - 3, Fig - 3). This was almost similar to the findings observed by Gosmanova EO et al, 2014 in which the mean age was 31.6 years[137]. In the present study males presented with renal impairment at an earlier age as compared to females. Seppi et al 2016 stated that estrogen may confer a protective resistant against renal injury[150].

Out of 50 cases of SCD with renal impairment 17 (34%) were kulta, 13 (26%) were Schedule Caste and 8 (16%) were Gouda (Table - 4, Fig - 4). These observations were similar to that reported by Kar et al who stated the disease to be more prevalent in Kulta, Agharia, Sc. Caste and Gouda[22].

Regarding the clinical presentations in patients of SCD with renal impairment most frequent complaints was painful episodes in 70%, followed by polyuria in 36%, fever in 24%, nausea in 10% and vomiting in 10% cases (Table - 5, Fig - 5). Clinical signs observed in these patients revealed that the most common sign was pallor in 92% followed by jaundice in 42%, puffiness of face in 42%, pedal edema in 28% and ascites in 10% of cases (Table - 5, Fig - 5). Power et al (1991) reported anaemia in 74% cases of SCD with nephropathy which was nearly similar to that of our study[128].

Hepatomegaly was found in 32% of cases, splenomegaly in 58% cases, and both hepatosplenomegaly in 22% of cases (Table - 6, Fig - 6). Kar et al reported splenomegaly in 66.2% of cases of SCD which is nearly similar to that of our study[22]. This is in contrast to studies from West and African countries where splenomegaly is unusual after 6-8 years of age due to autosplenectomy[1].

In the present study, 58% of patients with SCD and renal impairment had severe anaemia, the haemoglobin level being <6gm/dL ; 38% of patients had moderate anaemia with Hb level in between 6-10 gm/dL. The mean haemoglobin concentration in SCD with renal impairment was found to be 6.07 gm/dL (Table - 7). Similar observations was reported by Morgan et al. In their reports of SCD with nephropathy the mean haemoglobin concentrations was 5.6 gm/dL and this low haemoglobin concentration had a strong correlation with degree of renal insufficiency[82].

The mean Haematocrit in SCD with renal impairment was found to be 17.84%. Similarly the mean total leukocyte count and platelet count was 10.97 $x10^3$/cmm and 207.9 $x10^3$/cmm respectively (Table - 8). Similar observations were reported by da Silva GB et al, 2011, with mean haematocrit, TLC and PLT to be 18%, 7.9$x10^3$/cmm and 222.2$x10^3$/cmm respectively[65].

Excluding two cases who had SCD hepatopathy with very high bilirubin value, rest of the study subjects had a mean value for serum total bilirubin, direct bilirubin and indirect bilirubin was 2.24 mg/dl, 0.77 mg/l and 1.42 mg/dl respectively and mean values of AST, ALT and ALT were 45.8 IU/L, 28.2 IU/L and 137.94 IU/L respectively. In two cases who had SCD with hepatopathy the mean serum total bilirubin was 22.29mg/dL, mean serum indirect bilirubin was 4.56mg/dL and mean direct bilirubin was 17.72mg/dL. The mean AST, ALT and alkaline phosphatase were 937 IU/L, 523.5 IU/L, 497.5 IU/L respectively in cases of hepatopathy. We could not find a study relating to liver function test changes in patients of SCD with nephropathy. (Table - 9)

In our study of cases with SCD with nephropathy, the mean serum uric acid level was found to be 7.79 mg/dL(Table - 10). 70 % of patients in our study were hyperuricemic. Our findings were same as that of Jeffrey D Lebensburger et al, 2018 who stated in their study hyperuricemia may play a role in SCA nephropathy[99]. Though most studies states red cell turnover to be an important cause of hyperuricemia in sickle cell disease pateints, we could not find the exact cause of hyperuricemia in our patients. Further studies may clarify this aspect.

Normal blood pressures was noted in 84% of SCD patients with renal impairment where as 6% were in prehypertension stage and 10% of patients were in stage 1 of hypertension (Table - 11). This findings is in continuance with that of Giorgio et al. He reported all those patients having hypertension had renal failure[127]. Power et al, 2002, noted that hypertension preceded the diagnosis of renal failure in patients with SCD in 36% of the patients, which also supports our findings[128].

In our study the mean serum Na^+, K^+ and Ca^{++} levels among cases were found to be 135.34, 4.05 and 0.95 mmol/L. We found hypokalemia in 14% and hyperkalemia in 6% of patients (Table - 12). This was similar to that observed by da Silva GB et al, 2011[65]. They found the mean Na^+ and K^+ to be138 and 4.3 mmol/L respectively.

The mean fetal haemoglobin level in patients of SCD with renal impairment was found to be 17.76%(Table-13).The range of HbF varied from 11.3 to 23.1%. Studies evaluating the effect of haemoglobin F levels on SCD- related nephropathy, have not yet been performed. We found a positive correlation between the fetal haemoglobin level and eGFR value using Pearson correlation coefficient (r) being 0.3671 and P value of 0.009, which is statistically significant. This is an important observation in this study where evidence of a protective role of HbF is demonstrated. (Fig - 7)

Haematuria was detected in 5 (10%) patients of SCD with renal impairment in the present study (Table - 14). Falk et al, reported 11% haematuria in patients with sickle cell disease[125]. The observation of haematuria nearly same as that of Falk et al. Pyuria was found in 12 (24%) of cases (Table - 14). This indicates that significant number of patients with sickle cell disease with nephropathy have pyuria. Though we could not evaluate the cause of pyuria in our patients due to prior antibiotic use, Powers D.R. reported the relative risk of urinary tract infections in patients with renal failure when compared with patients without renal failure[138].

In the present study all the 50 patients of SCD with renal impairment had proteinuria of more than 150 mg in 24 hours. Out of these 50 patients of sickle cell nephropathy the proteinuria range was within 150-500 mg in 31 (62%), 500-1000mg in 10 (20%) cases, 1000-2000 mg in 4 (8%) cases, 2000-3000 mg in 2 (4%) cases and 3 (6%) cases had nephrotic range proteinuria (>3gm of protein in 24 hours). The mean protein excretion in these patients was 1075.56 mg in 24 hours. The mean protein excretion in those with nephrotic range of proteinuria was 7990 mg in 24 hours. (Table - 15, Fig-8). The first report dealing with the prevalence of proteinuria in sickle cell anaemia patient was that of Handerson (1950) who reported 31% prevalence in 54 patients[123]. Sklar et al, (1990) reported proteinuria in 20.6% (78 out of 368 patients)[130]. Falk et al, (1992) reported proteinuria in 22.8% (87 out of 381) patients. Falk reported in his study that 42 % of his patients had proteinuria in the range of 300 mg, 31% had upto 1000 mg, 17% had upto 3000 mg and 10% had upto 20,000 mg in 24 hours[125].

The incidence and degree of proteinuria in our patients of sickle cell disease with nephropathy was low compared to above authors. This is probably because of decrease severity of the disease in our subset of patients with high fetal haemoglobin. It is also interesting to state that all patients in the present study were receiving Hydroxyurea either regularly or irregularly which is in line with other studies where a protective role of hydroxyurea for proteinuria have been confirmed.

In our study it was seen that microalbuminuria (30-300mg/g) was detected in 37 (74%) of patients while macroalbuminuria (>300mg/g) was seen in 8 (16%) of patients (Table -16, Fig -9). Guasch et al. found that 68% of 300 SCD adult patients had high rates of urinary albumin excretion, with 26% of these patients displaying macroalbuminuria (defined as urine albumin excretion rate>300mg/g creatinine), which was almost similar to that of our study[122].

While beginning the study, mean blood urea, serum creatinine and eGFR in our study were 47.6 mg/dL, 2.1 mg/dL and 41.75 ml/min/1.73 m2 respectively . At end of the study the mean blood urea, serum creatinine and eGFR were 85.84 mg/dL, 3.09 mg/dL and 31.06 ml/min/1.73m^2 respectively. This showed a progressive decline in the eGFR value over a period of 24 months, with all patients in grade 3b of chronic kidney disease. It was observed that the decline in mean eGFR at beginning and after two years was nearly 10ml/min/1.73m^2 (Table 17-19, Fig 10-12). Vimal K. Derebail et al, 2018 also found a progressive decline in estimated GFR in patients with sickle cell disease[126]. There was also increase in the levels of blood urea and serum creatinine as noted in this study.

In our study, the ultrasonogram findings of kidneys in patients of SCD with features of renal impairment. It was found that 80% of cases have a normal kidney size whereas 16% have a decrease in their kidney size. Cortico-medullary differentiation (CMD) was diminished in 28% of cases and Cortical Echogenicity was increased in 44% (Table - 20). No definite calyceal abnormalities were found although we could not do intravenous pyelography. Our findings are unlike that of Mc Call et al, who reported enlargement of kidney in 10% case may be because we have included only adults in our study[102]. Small and contracted kidney has been reported by Sergeant G.R. et al, although they have not mentioned the exact percentage of case having similar findings[102]. From the present findings USG screening for kidney size alone cannot effectively detect renal impairment.

In our study, it was found that 23 patients (46%) were on a regular hydroxyurea therapy and 27 patients (54%) were on irregular hydroxyurea treatment. Further investigations is needed to determine whether HU prevent overt SCD progressing to chronic kidney disease or it should be indicated for sickle cell disease with albuminuria. (Table – 21, Fig-13)

VI. Summary

In the present study from November 2017 to October 2019, an attempt had been made to assess the different renal impairment in patients of sickle cell disease and observe the decline in renal function over a period of time in VIMSAR, Burla.

Fifty patients of homozygous sickle cell disease presenting to us with various forms of renal impairment were enrolled in the present study with timely followup of these patients in each four month intervals to note any progression and severity of the disease.

Majority of cases (64%) in this study were in the age group of 26-45 years with a significant predominance of SCD with nephropathy among male patients who presented at an earlier age as compared to their female counterpart. The mean age of patients in the present study was 36.18 years.

Sickle cell disease with nephropathy was more prevalent among Kulta (34%) followed by Scheduled Caste (26%) and Gouda (16%).

Among the presenting symptoms in patients of sickle cell disease with renal impairment the most common complaint was painful episodes (70%) followed by polyuria (36%) and fever (24%). Clinical examination revealed pallor in 92% followed by jaundice and facial puffiness in 46% and 42% respectively.

Splenomegaly was a common finding in patients of sickle cell disease with renal impairment in western Odisha and account for 58% of cases. Hepatomegaly was found in 32% of cases while 22% had both hepatosplenomegaly.

Ninety two percent of patients in the present study were anemic with 58% of them were severely anemic and 38% were having moderate anemia. The mean fetal haemoglobin was 17.76% and this too was an important finding in our study showing HbF concentration had a strong inverse correlation with renal insufficiency in sickle cell disease.

In the present study it was seen that 70% of patients were hyperuricemic with a mean value of 7.79 mg/dl. It can be inferred that hyperuricemia may play in sickle cell nephropathy.

Most patients (84%) of SCD with renal impairment have a normal blood pressure. Patients in prehypertension stage and stage 1 of hypertension were 6% and 10% respectively.

Hematuria was detected in 10% and pyuria in 24% of patients of sickle cell disease with renal impairment.

In the present study all patients of sickle cell disease with renal impairment have 24 hours protein excretion of >150mg, with a mean value of 1075.56 mg/24 hours. Maximum number (62%) of cases excreting protein in the range of 150-500 mg/day. Six percent of cases had a nephrotic range proteinuria of >3000 mg in 24 hours with a mean of 7990 mg/day.

Microalbuminuria was a significant finding observed in our study among sickle cell disease with renal impairment. Seventy four percent of cases have microalbuminuria in the range of 30-300 mg/g of creatinine while 16% of patients were having macroalbuminuria with >300mg/g creatinine.

At the initial evaluation the mean blood urea, serum creatinine and eGFR in our study were found to be 47.6 mg/dl, 2.1 mg/dl and 41.75 ml/min/1.73m^2 respectively. At the end of the study the mean blood urea,

serum creatinine and eGFR were 85.84 mg/dl, 3.09 mg/dl and 31.06 ml/min/1.73m^2 respectively. In the present study, patients of SCD with renal impairment showed a gradual decline in mean eGFR value with a difference of 10ml/min/1.73m^2 at the beginning and after two years of observation.

In the present study of patients of sickle cell disease with renal impairment, the ultrasonogram findings of kidney showed that 80% of cases had a normal kidney size with 28% showing diminished cortico-medullary differentiation and increased cortical echogeneicity in 44% of cases. From the present findings USG screening for kidney size alone cannot effectively detect renal impairment.

In our present study all patients were on hydroxyurea therapy either regularly or irregularly inferring a doubtful role of hydroxyurea in providing protection against renal impairment.

VII. Conclusion

Sickle cell disease is one of the important cause of deterioration in renal function in patients attending our institute.

Their may be a geographical distribution of renal insufficiency in patients of sickle cell disease as observed in the present study. SCD with features of renal impairment is particularly prevalent in males with an early age of predisposition as compared to females. So, timely monitoring of renal status and periodic followup should be instituted in patients of sickle cell disease at an early age.Various types of renal impairment observed in the present study on urine examination were polyuria, hematuria, leukocyturia, casturia, proteinuria and microalbuminuria, nephrotic range proteinuria. Chronic kidney disease is an important and early cause of morbidity in patients of sickle cell disease.

Fetal haemoglobin level had a strong inverse correlation with renal insufficiency in sickle cell disease suggesting a protective effect in patients of sickle cell disease with renal impairment.

The eGFR showed a progressive and relatively rapid decline in patients of sickle cell disease with renal impairment. So eGFR should be monitored in all patients with sickle cell disease and renal impairment.

The protective role of Hydroxyurea in preventing renal insufficiency needs a further extensive study. Repeated vaso-occlusive crisis, fever, vigorous outdoor activities may accelerate the progression of renal impairment but again needs to be explored further for establishing this relation.

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