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ORIGINAL ARTICLE

Biochemical Indicator of Sickle Cell Disease: Preliminary Report from India

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Abstract Blood biochemistry has significant effect on pathophysiology of human body. Recently few studies found the association of biochemical abnormalities in sickle cell patients. Sickle cell disease showed clinical variability where African ancestors have severe phenotype than Indian sicklers. Our aim was to evaluate the biochemicals in sickle cell patients and their effect on severity. Here we present the comparative biochemical levels in sickle cell patients as well as controls. Sickle cell patients diagnosed by HPLC and biochemical analysis done by Beckman-auto analyzer. T test applied for statistical analysis. Result showed the renal abnormality lesser in patients and related biochemical within the normal range and statistically not significant. Electrolytes, hepatic enzymes, alkaline phosphatase and glucose were elevated and statistically significant (P value <0.05). Observation of the study concludes the biochemical abnormality play a significant role in sickle cell patient's physiopathology and can be used to management of the disease.

Keywords Sickle cell anaemia · Biochemical · High performance liquid chromatography

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Introduction

Biochemical abnormalities have been associated with sickle cell disease (SCD) [1]. SCD is a hereditary disorder of hemoglobin synthesis that can affect the skeletal system owing to accelerated hematopoiesis and bone infarction [2]. Bone changes are common in SCD but the pathogenesis is not fully understood [3]. The level of alkaline phosphatase indicates severity of bone damage and is a useful guide of progress in the management of bone pains in sickle cell anaemia [4]. Bone disease with osteoporosis and osteomalacia are common in SCD. Some patients have vitamin D deficiency and low bone mineral density. The role of vitamin D and calcium supplementation to restore bone health in SCD has not been well studied [5]. SCD is associated with impaired urinary potassium excretion. Many renal structural and functional abnormalities have been associated with SCD [6]. Total protein concentration is determined by the nutritional state, hepatic function, renal function, and various disease states and hydration. Contribution of bone turnover to the hyper-catabolic state observation in sickle cell anemia is unknown while a study state the increased rates of bone turnover contribute to the increased rates of protein turnover and energy expenditure observed in adolescents with homozygous sickle cell anemia [7]. Previous studies performed in sickle cell patients confirmed that abnormal liver tests are common in patients. Hepatic dysfunction is a commonly recognized complication of SCD due to multiple factors such as intra-hepatic sinusoidal sickling, bilirubin gallstones, transfusion-related hepatitis infections or excess iron deposition [8–10]. Elevated aminotransferase levels are commonly associated with compromised hepatic integrity from various pathophysiology. In SCD, aspartate transaminase (AST) is released via intravascular hemolysis [11]. Serum creatinine

may be associated with renal insufficiency in sickle cell patients. When serum creatinine is elevated the disease has reached an advanced stage and lead to renal failure [12]. The balance of electrolytes (Na^+, K^+, Cl^-, HCO_3) in the body is essential for the normal functioning of the cells and organs. In sickle cells, an abnormal activation of potassium chloride (K^+Cl^-) co-transport system was proposed to be involved in cell potassium (K^+) loss and dehydration [13]. Deoxygenation of sickle cell is known to increase cation permeability of sodium (Na^+), potassium (K^+) and calcium (Ca^{2+}) [14, 15]. Urea, an end product of protein metabolism, is excreted by the kidney. Blood urea nitrogen directly related to protein intake and nitrogen metabolism and inversely related to the rate of excretion of urea. Urea concentration in glomerular filtrate is the same as in plasma, but its tubular re-absorption is inversely related to the rate of urine formation. Urea may play a significant role in the precipitation of sickling crisis [16]. AST:ALT (Alanine Aminotransferase) ratio may play role as a hemolytic marker, because it has an inverse association with the hemoglobin level. Whether in steady state or in crisis, provided hepatic and cardiac integrity has not been compromised, subjects with SCD would have higher AST levels due to the hemolytic nature of the condition [11]. Plasma hexose sugar levels and metabolism are altered in SCD. The essential dependence of the erythrocyte on glycolysis for its metabolic energy, as well as the central role of glucose as the central energy nutrient of the body makes this alteration a fundamental problem that could account for some of the observed lesions of SCD [17]. It has previously been reported that in adult patients with sickle-cell anemia the serum phosphate value and the maximum tubular re-absorption of phosphate per liter of glomerular filtrate (TmP/GFR) significantly higher than in normal controls. The lower serum phosphate value and TP/GFR in younger sicklers seems to be in contrast with the relatively high serum phosphate value and TP/GFR previously reported in adults with sickle cell anemia [18]. In sickle cell anemia the shortened survival of red blood cells presents the liver with an augmented load of bilirubin for hepatic clearance [19]. Uric acid is an end product of nucleoprotein metabolism and is excreted by the kidney. An increase in serum uric acid concentration occurs with increased nucleoprotein synthesis or catabolism or decreased renal excretion. It poses a special problem for humans because of its limited solubility, particularly in the acidic environment of the distal nephron of the kidney [20]. Hyperuricemia occurs only in patients who develop altered renal tubular function with diminished urate clearance secondary to diminished urate secretion [21]. In India the paucity of information on the roles of these biochemicals in the pathogenesis and management of SCD. Thus our aim was to evaluate the biochemical level in sickle cell patient and correlate with the severity of disease.

Materials and Methods

Subject were Sickle cell patients; attending the haematology Outpatient Department (OPD),All India Institute of Medical Sciences, New Delhi. Age sex matched 150 healthy individual were selected to compare the biochemical level. Control population were chosen from the healthy relatives of patients who had never diagnosed any disease. About 6 ml blood sample collected after taking signed consent from patient as well as controls. This study was approved by institutional ethical committee. Forty-five sickle cell anemia patient and 60 sickle β-thalassemia patient were diagnosed by high performance liquid chromatography (HPLC-Bio-Rad-Variant^{TM} from Bio Rad, CA, USA) using Bio-Rad diagnostic kit. Complete blood count and red cell indices were measured by automated analyzer (SYSMEX K-4500, Kobe Japan) using Transasia diagnostic kit. All biochemical investigation was done by Beckman-CX-4 and CX-9 auto analyzer using Randox diagnostic kit. *t* test used to compares the means of two groups on GraphPad (version 3.06) software. The *P* value <0.05 was considered statistically significant.

Result

Sickle cell patients were categorised in two groups. First group had 50 sickle cell anemia (32 male and 18 female with mean age 11.2 ± 5.4) while second group had 70 sickle cell β-thalassemia patients (46 male and 24 female with mean age 11.8 ± 5.5). Age–sex matched 150 controls (87 male and 63 female with mean age 12.3 ± 6.2) were characterized to compare the patients investigated values. Blood chemistry profile with electrolytes; BUN, creatinine, uric acid, calcium, sodium, potassium phosphate, AST, ALT, bilirubin, alkaline phosphatase, random glucose and total protein evaluated in patients group as well as controls. Renal insufficiency related variables were evaluated and observed the value were lower than the controls observed value however they were not statistically significant. *P* value of urea, phosphate and creatinine was 0.5 while the uric acid *P* value was 0.08. Calcium and sodium levels were significantly low in sickle patients (*P* value <0.001) while potassium level was significantly high in sicklers (*P* value <0.001). Details of comparative value are given in Table 1. Total protein, random glucose, AST, ALT, total bilirubin and alkaline phosphatase were significantly elevated in sickle cell patient (*P* value <0.001). These observed value were high in sickle cell anaemia patient in

Table 1 BUN and electrolytes levels in sickle cell patient

Parameters	Mean ± SD			*P* value
	HbSS $N = 50$	HbSβ-thal $N = 70$	Control $N = 150$	
Urea (mg%)	30.2 ± 17.5	32.5 ± 15.4	38.9 ± 13.9	0.523
Creatinine (mg%)	1.2 ± 0.4	1.3 ± 0.3	1.4 ± 0.2	0.513
Phosphate (mg%)	2.6 ± 1.7	2.1 ± 0.8	2.8 ± 1.6	0.516
Uric acid (mg%)	3.2 ± 1.2	2.6 ± 0.9	3.60 ± 1.2	0.088
Calcium (mg%)	6.2 ± 1.9	6.5 ± 1.7	8.36 ± 1.04	<0.001
Sodium (mEq/l)	114.7 ± 18.6	117.8 ± 11.5	128.6 ± 9.2	<0.001
Potassium (mEq/l)	4.8 ± 1.4	4.7 ± 1.8	3.9 ± 1.7	<0.001

Table 2 Glucose, total protein and Hepatic enzyme levels in sickle cell patient

Parameters	Mean ± SD			*P* value
	HbSS $N = 40$	HbSβ-thal $N = 60$	Control $N = 150$	
Total protein (gm%)	7.1 ± 0.7	6.8 ± 0.8	6.2 ± 1.2	<0.001
Glucose (R) (mg%)	93.9 ± 30.6	93.2 ± 20.4	87.7 ± 18.6	<0.001
AST (I.U.)	69.6 ± 25.9	49.5 ± 19.6	37.1 ± 12.2	<0.001
ALT (I.U.)	37.4 ± 15.2	31.7 ± 13.7	32.2 ± 9.1	<0.001
Alkaline phosphatase (I.U.)	679.2 ± 117.5	667.5 ± 149.1	573.7 ± 131.5	<0.001
Total bilirubin (mg%)	3.2 ± 1.3	2.5 ± 1.4	0.7 ± 0.4	<0.001

compression to sickle cell β-thalassemia patients. Details of the comparative value are given in Table 2.

Discussion

The clinical manifestation of sickle cell anemia in India seems to be milder than in Africa and Jamaica [22]. The clinical spectrum of SCD ranges from mild to severe liver function and clinical crises with marked hyperbilirubinemia and liver failure. Multiple factors may contribute to the etiology of the liver disease, including ischemia, transfusion related viral hepatitis, iron overload, and gallstones [23]. Delayed growth and bone destruction may contribute to the elevated levels of alkaline phosphatase. Higher levels of alkaline phosphatase may be due to associated vasoocclussive crises involving the bones rather than pathology of the liver [24, 25]. The level of the heat-labile alkaline phosphatase indicates severity of bone damage and is a useful guide of progress in the management of bone pains in sickle cell anaemia [4, 26]. We report the significant elevation of alkaline phosphatase in sickle cell patient (*P* value <0.001) where the 16.7% patients clinically present the bone related abnormalities. Mean value of alkaline phosphatase was 679.2 ± 117.5 I.U. in sickle homozygous while 667.5 ± 149.1 I.U. was in sickle β-thalassemia patients. The entire studied subjects were <18 years. Endogenous creatinine is excreted by filtration through the glomerulus and by tubular secretion. Clinically creatinine clearance is an acceptable measure of glomerular filtration rate (GFR) but sometimes over estimates GFR. Patients with sickle cell anemia or sickle cell trait may present several types of renal dysfunction [27]. The GFR in homozygous SCD is supra-normal in childhood but falls steeply with age, often culminating in renal failure [28]. Few studies report the elevation of uric acid and considerably lower urea and creatinine in the SCD patients [16, 29, 30]. Hyperuricemia was encountered in several studies on SCD patients. It was suggested that an excessive level of uric acid pool due to an increased marrow activity and turnover of nucleic acids. These conditions were associated with many diseases including hemolytic anaemia and certain haemoglobinopathies [31, 32]. In our cases; blood urea was low in sickle cell patient in compression to controls. The mean value of urea was 30.2 ± 17.5 and 32.5 ± 15.4 mg% in sickle homozygous and sickle β-thalassemia, respectively. However the variable was not significant (*P* value 0.523). Creatinine levels were similar in the sickle homozygous and sickle β-thalassemia patients as well as controls. The creatinine level was not statistically significant (*P* value 0.513). The value of creatinine was 1.2 ± 0.4 and 1.3 ± 0.3 mg% in sickle homozygous and sickle β-thalassemia patients respectively. Blood phosphate (*P* value 0.516) and uric acid (*P* value 0.088) levels were similar in patient as well as controls and statistically not significant. The observed value of phosphate was 2.6 ± 1.7

and 2.1 ± 0.8 mg% in sickle homozygous and sickle β-thalassemia patients respectively while the 2.6 ± 0.9 and 3.2 ± 1.2 mg% uric acid was reported in sickle homozygous and sickle β-thalassemia patients. These observations suggest the renal insufficiency is uncommon in Indian sicklers where out of 120 sickle cell patients, only three were clinically present renal abnormality. RBCs from SCD patients have elevated cation permeability and a deoxygenation-induced cation conductance which mediates Ca^{2+} entry, providing an obvious link with phosphatidylserine exposure [33]. Various study reported the significant low level of calcium in sickle cell patients [34, 35]. A study find the increase level of potassium and decrease concentration of sodium in the sicklers in compression to controls [36]. Potassium abnormality seen in sickle cell patient with renal insufficiency [37]. Sodium–potassium pump in erythrocytes indicate a magnified role in the pathophysiology of sickle cell erythrocytes and suggest that its inhibition might prove useful in therapy [38]. Level of sodium and calcium were significantly lower in our sickle cell patients (P value <0.001). Sodium level was 114.7 ± 18.6 mEq/l in sickle homozygous while 117.8 ± 11.5 mEq/l was in sickle β-thalassemia patients. Calcium level was 6.2 ± 1.9 mg% in sickle homozygous patients and 6.5 ± 1.7 mg% was in sickle β-thalassemia patients. Potassium level was significantly higher in sickle cell patients than control (P value <0.001). Mean potassium level was 4.8 ± 1.4 mEq/l in sickle homozygous and 4.7 ± 1.8 mEq/l in sickle β-thalassemia patients. Liver abnormality release aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which makes useful test for detecting liver damage. Hemolysis also raises AST and ALT levels in SCD [11, 39]. Elevation of serum phosphate found in sickle cell patients explain the phosphate re-absorption in patients [40]. Bilirubin is a compound produced by the breakdown of hemoglobin from red blood cells. When levels are abnormally high it indicates liver dysfunction such as cirrhosis, hepatitis, gallstones or blood disease such as sickle cell anemia. Sickle cell anemia affects the blood; patients can experience high bilirubin levels. Few study report the elevation of bilirubin in SCD [41, 42]. A study report the increased level of total protein in sickle cell patients [42]. The carriers of the sickle cell gene could be more susceptible to impaired glucose metabolism and other disease conditions tied to the observed alteration in the patterns of metabolism of hexose sugars. Degree of blood hexose concentration alteration can be investigated as possible biomarker for sickle-cell anemia intensity [17]. A Study also found the increased level of glucose in sickle cell patient than control [43] while another study reported marginally higher glucose intolerance in children with sickle cell anaemia [44]. Hepatomegaly (25.8%), splenomegaly (27.5%) and gall bladder stone (25%) were frequent in our cases. AST and ALT level were significantly elevated in sickle cell patient (P value < 0.001). Mean AST level (69.6 ± 25.9 I.U.) was higher in sickle homozygous than sickle β-thalassemia patients (49.5 ± 19.6 I.U.). ALT level was also higher in sickle cell homozygous (37.4 ± 15.2 I.U.) than sickle cell β-thalassemia patients (31.7 ± 13.7 I.U.). Total bilirubin, total protein and random glucose were significantly elevated in sickle patient (P value <0.001). The level of total bilirubin was 3.2 ± 1.3 and 2.5 ± 1.4 mg% in sickle homozygous and sickle β-thalassemia patients, respectively. Total protein was higher (7.1 ± 0.7 gm%) in sickle homozygous than sickle β-thalassemia (6.8 ± 0.8 gm%). The level of random glucose was 93.9 ± 30.6 mg% in sickle homozygous and 93.2 ± 20.4 mg% in sickle β-thalassemia patients.

Conclusion

The observation of the study concludes the renal insufficiency is not common in Indian sickle cell patients while the abnormality of electrolytes present significantly in sickle patients. AST:ALT ratio and alkaline phosphatase significantly elevated and can be used as bio-markers. Glucose, total protein phosphate also found higher in Indian sickle cell patients. The finding of studies state the biochemical abnormality play a significant role in sickle cell patients physiopathology and can be used to management of the disease.

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