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# Impact Assessment of Foetal Haemoglobin on Biochemical Markers of Liver Function in Sickle Cell Disease Patients

**Mathias Abiodun Emokpae, Rossy Jane Umeadi**

Department of Medical Laboratory Science, School of Basic Medical Sciences, College of Medical Sciences, University of Benin, Benin City, Nigeria

**Email address:**
biodunemokpae@yahoo.com (M. A. Emokpae)

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**Abstract:** *Background/objective:* The role of foetal haemoglobin (HbF) on the modulation of clinical manifestations in sickle cell disease is well known but there is inconsistency as to the levels of HbF that may protective against the development of liver disease. This study evaluates the impact of HbF on biochemical markers of liver function in sickle cell disease (SCD) patients in steady clinical state. *Materials and Methods:* Liver function tests: aspartate amino transferase, alanine amino transferase, alkaline phosphatase, bilirubin and proteins as well as HbF were assayed in SCD patients using colorimetric methods. *Results:* Out of 100 SCD patients, 24% had high (>5%) HbF while 76% had low (<4.9%) HbF levels. Those subjects with high HbF had lower ($p<0.001$) levels of measured variables except albumin which was higher compared to levels in those with low HbF. HbF correlated negatively with the measured variables except albumin. *Conclusion:* The SCD patients with high HbF had lower levels of the measured variables compared to those with low levels of HbF. High HbF levels (>5%) may be protective against the development of liver pathology in SCD patients in steady clinical state.

**Keywords:** Foetal Haemoglobin, Liver Disease, Liver Function Tests, Sickle Cell Disease, Steady Clinical State

## 1. Introduction

Sickle cell disease (SCD) is an inherited multisystem disease characterized by chronic haemolyticanaemia and vaso-occlusive crisis which often results in vascular occlusion of micro-vascular vessels by sickled red blood cells leading to multi-organ infarction. It is a condition which has autosomal recessive pattern of inheritance from parents, in which the red blood cells assume an abnormal, rigid, sickle shape in deoxygenated state[1-2]. The degree of HbS polymerization in the circulation determines how likely the individual is to have a vaso-occlusive crisis or other adverse event. This causes it to become trapped, thus blocking small vessels of the microcirculation[3-4].

Liver pathology is a common complication due to the disease itself and its treatment[5-8]. In addition to the vascular complications from the sickling process, patients with SCD may have received multiple transfusions, placing them at risk for viral hepatitis and iron overload. All these conditions combined with the effects of chronic hemolysis resulting in the development of pigment gallstones which ultimately may lead to liver disease[7]. In SCD patients, mild to moderate hepatomegaly develops early, followed by shrinkage produced by fibrosis and cirrhosis[9-10]. Hepatic tenderness occurs occasionally, patients with sickle cell anaemia may suffer from a variety of hepatic alterations. The altered shape of red blood cell favours intravascular haemolysis and thus occlusion of the liver vascular bed, leading ultimately to tissue injury which ranges from asymptomatic mild liver function test abnormalities to severe acute damage[11].

It is of interest to note that cells are less prone to sickling in individuals who retain a high level of foetal haemoglobin (HbF). Haemoglobin F inhibits the polymerization of the HbS owing to its high oxygen affinity[12]. Haemoglobin F dissociates to a dimer, which when combined with HbS, gives a tetramer that does not form a polymer. This is in contrast to HbA, which dissociates to a dimer that combines to give a tetramer that has a 50% chance of polymerizing. It is well recognized that high levels of HbF in SCD patients modulate the clinical manifestations of the disease. The role of HbF on the clinical phenotype is variable and inconsistent; for example HbF levels close to 20% may be found in patients with severe disease[4,13]. The modulation of symptoms

and complications becomes more consistent when a certain level of HbF threshold has been achieved. The threshold for significant reduction in acute episodes of pain, chest syndromes, and priapism is 20%, and for organ damage 10%[3]. The symptoms of sickle cell disease (SCD) are almost completely eliminated with HbF levels above 25%; however, studies indicated that any increment in HbF level may improve the overall survival[13-14]. There is however controversy as to the amount of the HbF that may be required to protect the patients from organ damage in our environment and impact of HbF on liver function tests has not been assessed. Therefore, this study evaluates the biochemical markers of liver function in SCD patients in steady clinical state and the protective effect of HbF on the levels of these biochemical markers.

# 2. Materials and Methods

This descriptive case control study was conducted at the Department of Medical Laboratory Science, College of Medical sciences, University of Benin. The protocol for the study was reviewed and approved by the Edo state Ministry of Health, Benin City before the commencement of study. Informed consent was obtained from all subjects who participated in the study. The subjects included sickle cell disease patients on routine visit to Sickle Cell Centre, Benin City. A total of 150 samples were analyzed which comprised of 100 SCD patients (HbSS) and 50 controls (HbAA).

*Inclusion criteria:* All SCD patients on steady clinical state without acute illness such as vaso-occulusive crisis, acute chest pain syndrome or bacterial infection were included in the study. The control subjects were apparently healthy HbAA subjects.

### *2.1. Exclusion Criteria*

All SCD patients with acute illness such as vaso-occlusive crises, acute chest syndrome or bacterial infection were excluded from the study. Subjects with other haemoglobinopathies were also excluded.

### *2.2. Sample Collection*

Five millilitres of blood was collected aseptically and 2mL aliquot was dispensed into EDTA container and 3mL aliquot was emptied into a plain container. The anticoagulated blood was used for HbF estimation using alkaline denaturation method[15]. The non anticoagulated blood was spun at 1500rpm for 10minutes and the supernatant serum was separated into a separate tube. The serum was stored at -20$^0$c for 2weeks prior to analysis. The biochemical markers of liver function assayed were Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatise (ALP), bilirubin, protein and albumin. They were analyzed with spectrophotometric methods using commercially available reagent kits supplied by Randox laboratories, UK.

### *2.3. Statistical Analysis*

The data obtained were statistically evaluated using Statistical Package for Social Sciences program (SPSS) version 16.0. Values obtained in this research were represented as mean and Standard error of mean (SEM) for both tests and controls. Student's *t* test was used to compare data at 95% confidence intervals ($p<0.05$).The measured variables were compared in test subjects with high and low HbF concentration and the biochemical markers of liver function were correlated with HbF in test subjects.

# 3. Results

Table 1 shows the mean levels of HbF, serum AST, ALT, ALP,AST/ ALT ratio, total protein, globulin, total bilirubin, conjugated bilirubin in both SCD patients and control subjects. HbF, serum AST, ALT, ALP, AST/ALT ratio, total protein, globulin, conjugated bilirubin, total bilirubin were significantly higher ($p<0.001$) in SCD patients compared with controls while albumin was lower ($p<0.001$) in SCD patients compared with controls.

***Table 1.*** *Biochemical markers of liver function in SCD patients and control subjects (mean ± SEM).*

| Measured variables | SCD patients HbSS | Subject with normal haemoglobin HbAA(controls) | P-Value |
|---|---|---|---|
| Number of subjects | 100 | 50 | |
| Number of males | 60 | 26 | |
| Number of females | 40 | 24 | |
| Age (yrs) | 24.25 ±0.86 | 23.28±0.24 | |
| Foetal haemoglobin(%) | 2.38±0.20 | 0.29±0.03 | 0.001 |
| Alkaline phosphatase(U/L) | 169.71±56.01 | 83.87±12.31 | 0.001 |
| Aspartate amino transferase (U/L) | 21.94±1.30 | 8.69±1.91 | 0.001 |
| Alanine amino transferase (U/L) | 15.38±0.97 | 10.07±0.25 | 0.001 |
| AST : ALT ratio | 1.78±0.13 | 0.86±0.02 | 0.001 |
| Total protein(g/L) | 88.34±1.19 | 66.86±0.48 | 0.001 |
| Albumin(g/L) | 33.37±0.66 | 40.42±0.51 | 0.001 |
| Globulin(g/L) | 54.97±1.56 | 27.44±0.50 | 0.001 |
| Conjugated bilirubin(μmol/L) | 17.13±1.05 | 3.42±0.17 | 0.001 |
| Total bilirubin(μmol/L) | 55.10±3.18 | 10.23±0.23 | 0.001 |

Table shows that ALP,AST, ALT, AST:ALT ratio, total protein, albumin, globulin, CB, and TB in SCD patients with high HbF as compared with those with low HbF. All measured variables except Albumin were significantly lower (0.001) while albumin is significantly higher (p<0.001) in subjects with high HbF than in those with low HbF levels.

***Table 2.*** *Biochemical markers of liver function in SCD patients with high (≥5%) and low (≤4.9%)HbF (mean ± SEM).*

| Measured variables | SCD patients with high HbF (≥5%) | SCD patients with low HbF (≤4.9%) | P-value |
|---|---|---|---|
| No of subjects | 24 | 76 | - |
| Foetal haemoglobin | 5.36±0.09 | 1.44±0.13 | 0.001 |
| Alkaline phosphatase (U/L ) | 84.24±4.06 | 196.69±3.52 | 0.001 |
| Aspartate amino transferase(U/L) | 8.53±0.43 | 26.18±1.38 | 0.001 |
| Alanine amino transferase (U/L) | 10.66±1.29 | 16.86±1.15 | 0.001 |
| AST: ALT ratio | 0.90±0.36 | 2.05±1.36 | 0.001 |
| Total protein (g/L) | 73.87±1.29 | 92.90±1.07 | 0.001 |
| Albumin (g/L) | 40.29±0.82 | 31.18±0.63 | 0.001 |
| Globulin (g/L) | 33.58±1.43 | 61.72±1.23 | 0.001 |
| Conjugated bilirubin(μmol/L) | 5.49±1.05 | 20.81±1.02 | 0.001 |
| Total bilirubin (μmol/L) | 12.18±0.45 | 68.65±2.70 | 0.001 |

***Table 3.*** *Correlation of HbF with measured markers of liver function in SCD patients.*

| Measured variables | r-value | p-value |
|---|---|---|
| Alkaline phosphatase (U/L ) | -0.77 | 0.001 |
| Aspartate amino transferase (U/L) | -0.51 | 0.001 |
| Alanine amino transferase (U/L) | -0.26 | 0.01 |
| AST: ALT Ratio | -0.33 | 0.001 |
| Total protein (g/L) | -0.61 | 0.001 |
| Albumin (g/L) | 0.52 | 0.001 |
| Globulin (g/L) | -0.68 | 0.001 |
| Conjugated bilirubin (μmol/L) | -0.62 | 0.001 |
| Total bilirubin (μmol/L) | -0.71 | 0.001 |

***Table 4.*** *Markers of liver function in male and female SCD patients (mean ± SEM).*

| Measured variables | Female SCD patients | MALE SCD patients | P-value |
|---|---|---|---|
| No of subjects | 60 | 40 | |
| Foetal Haemoglobin(%) | 2.42±0.25 | 2.32 ±0.31 | 0.79 |
| ALP(U/L ) | 168.42±7.31 | 171.62±8.81 | 0.78 |
| AST(U/L) | 22.52±1.75 | 21.08±1.93 | 0.59 |
| ALT(U/L) | 16.18±1.31 | 14.18±1.40 | 0.31 |
| AST-ALT ratio | 1.68±0.15 | 1.93±0.24 | 0.35 |
| Total Protein (g/L) | 87.87±1.63 | 89.05±1.73 | 0.63 |
| Albumin (g/L) | 33.75±0.82 | 32.80±1.09 | 0.48 |
| Globulin (g/L) | 54.12±2.10 | 56.25±2.33 | 0.51 |
| Conjugated Bilirubin (μmol/L) | 17.47±1.30 | 16.63±1.76 | 0.69 |
| Total Bilirubin (μmol/L) | 53.69±4.07 | 57.20±5.14 | 0.59 |

ALP=Alkaline Phosphatase; AST= Aspartate amino transferase ALT= Alanine amino transferase.

Table 3 shows correlation of HbF with ALP, AST, ALT, AST-ALT ratio, total protein, albumin, globulin, conjugated bilirubin and total bilirubin in SCD patients. HbF levels correlated negatively (0.001)with ALP, AST, AST-ALT ratio, total protein, globulin, conjugated bilirubin, total bilirubin and ALT(P=0.01) while HbF correlated positively(p<0.001) with albumin.

The table 4 shows the different levels of measured between male and female SCD patients. The differences were not statistically significant (p>0.05).

# 4. Discussion

Hepatic disorders in SCD may be due to sickling process, acute hepatitis or hepatic sequestration crisis. The frequency and Pathophysiology of liver disease in SCD is under debate[7]. Even though the etiology of liver disease is multifactorial, available evidence suggest the importance of vascular changes and the participation of sickling process was the major cause of chronic hepatic changes observed[7].The levels of measured biochemical variables in this study were higher

($p<0.001$) in SCD than control subjects except albumin which was lower ($p<0.001$) in SCD than controls. Twenty four percent (24%) of the study subject had persistent high (>5%) HbF while 76% had low (<4.9%) levels of HbF. The levels of the biochemical markers of liver function were lower in SCD patients with high HbF than those with low HbF ($p< 0.001$). Haemoglobin F correlated negatively with ALP, AST, ALT, AST:ALT ratio, total protein, globulin, conjugated bilirubin and total bilirubin but correlated positively with albumin. There was also no significant different in the levels of HbF and the other measured variables in female SCD patients compared to their male counterpart.

Raised levels of HbF were observed to increase survival in SCD patients[1] and therefore therapeutic induction of HbF (r-gene,HbG1, HbG2) expression is used in the management of SCD patients. However raised HbF only may not be sufficient to forestall complications associated with SCD, as some patients with increased HbF (upto 20%) were observed to have severe SCD manifestations[1]. A study in Jamaica, revealed that patients with high HbF has better haematological indices compared to those with low HbF[16]. Earlier studies did not however observe any association between HbF and disease severity[17-18]. It was suggested that the level of HbF needed to prevent acute clinical event was about 20% while levels of 10% was needed to prevent organ damage[18]. Twenty four (24%) of the study subjects had high HbF and is consistent with 29% reported previously in Sokoto, northern Nigeria[19].High level of HbF in the red blood cell of an individual tends to impair sickling at physiologic oxygen tension and may clinically improve the general well-being of the subject. Most of the SCD patients with high HbF are reported to be free from most of the severe clinical manifestations associated with SCD[19]. This may probably account for the lower levels of biochemical markers of liver function observed in this study.

The gender of the patients did not significantly affect the levels of the HbF but mean values was higher in female (2.42±0.25) than males (2.32 ±0.31), this agreed with that reportedbyAdekile and Huisman[20].They reported that female sickle cell patients with haplotypes 19/19 had higher HbF levels than their male counterparts, the same was observed for the patients with the 19/3 haplotype combination but not for those with the 20/3 haplotype combination. Gladwin et al[21] also reported that female patients have slightly greater HbF levels, which may be protective; and concluded that the basis for these differences could lie in the observation that nitric oxide bioavailability and responsiveness are reduced in males but not females with sickle cell disease. Nitric oxide is thought to be important in maintaining vasomotor tone, limiting platelet aggregation, inhibiting ischemia-reperfusion injury, and modulating endothelial adhesion molecule expression. Estrogens facilitate nitric oxide production and limit its consumption. In the same vein, Ikuta et al[22]linked nitric oxide to transcriptional control of HbF and could therefore contribute to gender differences in HbFexpression.

The mean HbF levels (2.38±0.20) observed in this study is consistent with (2.99± 5.16) reported in Sokoto[23] and (3.05 ± 1.61) reported in Calabar[24], it is however lower than (5.9± 3.8) reported in Ibadan[25].

There was significant increase in the mean values of ALP, AST, ALT and bilirubin in SCD patients when compared with control subjects. This observation is in agreement with previous reports that there is liver dysfunction in steady state sickle cell disease[26]. According to Kotilaet al[18], acute intrahepatic cholestasis or the extreme haemolysis which causes hyperbilirubinaemia, a common event in sickle cell disease is the cause of the increased ALP in these patients. Hemolysis also raises AST and ALT levels in SCD[27-29]. There was significant increase in the mean values of AST: ALT ratio in SCD patients when compared with control subjects, this is in agreement with Nsiahet al[27], they reported that there is increased AST: ALT ratio greater than 1 owing to the fact that there is presence of intravascular haemolysis in SCD. Abnormalities in liver function tests were reported in 27% of a group of 48 subjects[11]. Others had reported that abnormal liver function tests may be common in the absence of significant liver pathology[30], but recent studies have reported the presence of hepatomegaly in 40-80% of living SCD patients and 100% of cases in autopsy study[11,31]. The elevated levels of liver enzymes may be related to haemolysis and/or ineffective erythropoiesis. Serum ALT levels may accurately reflect hepatocyte injury while ALP which is of bone origin may also be elevated[31].

There was significant increase in the mean values of total protein, globulin in SCD patients when compared with control subjects, while albumin, was reduce in SCD patients with respect to control subjects, this is in accordance with Adu et al[32] who reported hyperproteinaemia in the sickle cell individuals as a result of hyperglobulinaemia which occur in these individuals due to the gamma (γ) globulin fraction. The increase gamma (γ) globulin is due to the extent of antigenic stimulation coming from the environment[33], also in another study, a high level of globulin in sickle cell homozygous individuals was reported[34]. Adenaikeet al[35] attributed this hyperglobulinaemia to increased erythrocyte destruction during sickling. This is in contrast to Famoduet al[36] who reported high level of albumin in sickle cell patients especially during vaso-occlusive crisis and Tripathi et al[37] who observed low levels of total protein and albumin in SCD patients.

HbFcorrelated negatively with serum ALP, AST, ALT, AST-ALT ratio, total protein, albumin, globulin, conjugated bilirubin and total bilirubin, in SCD patients. This negative correlation may indicate that high HbF may be protective against increased liver enzymes in patients with steady clinical state.

In conclusion, the measured biochemical markers of liver function were higher in SCD patients than controls except albumin which was higher in controls than SCD patients. The SCD patients with high HbF had lower levels of the measured variables compared to those with low levels of HbF. High HbF levels (>5%) may be protective against the development of liver pathology in SCD patients.

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