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Impact of Foetal Haemoglobin on Disease Severity among Sickle Cell Subjects

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Abstract

Objective: Haemolysis is a common complication of Sickle cell disease, exhibiting considerable variability among affected individuals. Established haemolysis markers including lactate dehydrogenase activity (LDH) and bilirubin have been reported as reliable indicators of disease severity. Foetal haemoglobin plays a pivotal role in Sickle Cell Disease by neutralizing Haemoglobin-S (HbS) polymerization, consequently extending the lifespan of red blood cells and influencing overall clinical outcomes. This study aims to investigate the impact of foetal haemoglobin on disease severity among sickle cell subjects.

Method: This study involved forty (40) sickle cell subjects and thirty (30) normal subjects. Blood samples from the participants were analysed for lactate dehydrogenase activity, bilirubin concentration, and foetal haemoglobin concentration. The alkali denaturation technique was employed for HbF analysis, while diagnostic kits were used for LDH and bilirubin assays.

Results: Foetal haemoglobin concentrations below 10% have been defined as low. The HbF concentration of the sickle cell subjects was relatively low (5.23%) but significantly higher than the normal subjects (1.84%). Similarly, there was a significant elevation in markers of haemolysis in the sickle cell subjects compared to the normal subjects. Subjects with HbF>10% demonstrated a noteworthy increase in haemolysis markers compared to those with HbF<5%. Additionally, a significant inverse relationship was observed between HbF concentration and haemolysis markers.

Conclusion: The study highlights a significant inverse correlation between foetal haemoglobin concentration and disease severity among sickle cell subjects and also contributes valuable insights to our understanding of sickle cell disease pathology.

Keywords: Sickle Cell Disease; Disease Severity; Foetal Haemoglobin Concentration; Haemolysis; Lactate Dehydrogenase Activity; Bilirubin Concentration

Abbreviations: SCD: Sickle Cell Disease; HbF: Foetal haemoglobin; HbS: Sickle haemoglobin; LDH: Lactate dehydrogenase.

Introduction

Sickle Cell Disease (SCD) is a hereditary blood disorder characterized by presence of a mutated form of haemoglobin (HbS) in the red blood cell [1]. The polymerization of HbS is a key trigger for all sickle cell related complications including haemolysis, organ failure, and painful crises [2]. Despite years of extensive research efforts, a definitive cure still remains elusive, and the disorder continues to pose significant global health burden. Annually, over 200, 000 cases of the disorder are reported with the majority originating from Africa [3].

The rate of tissue damage varies greatly in sickle cell subjects and is used as tool for assessing disease severity [4]. Lactate dehydrogenase (LDH), an enzyme found in cells throughout the body, and bilirubin, a product of haem catabolism are reliable haemolysis markers employed for assessing disease severity in sickle cell disease [5,6]. The polymerization of HbS and susceptibility of sickled cells to oxidative stress are key underlying factors responsible for the elevated rate of haemolysis in subjects with sickle cell disease [7].

Foetal haemoglobin (HbF) is the well-known modulator of sickle cell disorder, produced by sub-set of red blood cells known as F-cells. HbF possesses the ability to neutralize the polymerization effect of HbS and improve the clinical status of the individuals with SCD [8]. Individuals with a higher concentration of HbF, such as those from parts of Saudi Arabia are known to experience less severe disease complication compared to individuals with a lower concentration, like those from most parts of Africa [9,10]. Therefore, this study aims to investigate the impact of foetal haemoglobin on disease severity in individuals with SCD.

Methods

Subjects and Samples

This cross-sectional study comprised of forty adult subjects with Sickle Cell Disease (SCD) attending clinic at the Haematology department of Ahmadu Bello Teaching Hospital (ABUTH) Zaria, Nigeria. The study design received approval from the Health and Ethics Committee of the institution and recruited subjects consent was received to participate in the study. The eligibility criteria for inclusion in the study were as follows; Adults diagnosed with SCD who were not on hydroxyurea and had not received a blood transfusion within the last six months. Blood samples received from thirty normal subjects were used as control.

Analysis of Biomarkers

Venous blood sample (4mL) collected in a tube containing ethylenediaminetetraacetic acid (EDTA) anticoagulant was used for whole analysis. Plasma derived from the whole blood was employed for the analysis of markers of disease severity (Lactate dehydrogenase activity and bilirubin concentration). Diagnosis kits from Agappe and lab-kit were used for determination of bilirubin and LDH activity, respectively. Red blood cells obtained from whole blood was used for determination of foetal haemoglobin using the Betke alkali denaturation method.

Statistical analysis

Statistical analysis was carried out with Graph-pad prism (version 9.3.1). Skewness test was employed for the determination of data distribution. Descriptive data were presented as mean and standard deviation while students T-test and one-way ANOVA were used for comparing means across different groups. Linear regression was applied to assess the relationship between the biochemical parameters. Statistical significance was considered for all values within $P<0.05$.

Results

The Foetal haemoglobin concentration (Figure 1a), Lactate dehydrogenase activity (Figure 1b) and bilirubin concentration (Figure 1c) in sickle cell subjects (HbSS) and normal subjects (HbAA) were assayed. The foetal haemoglobin concentration, bilirubin concentration and lactate dehydrogenase activity were significantly elevated in sickle cell subjects compared to the normal subjects.

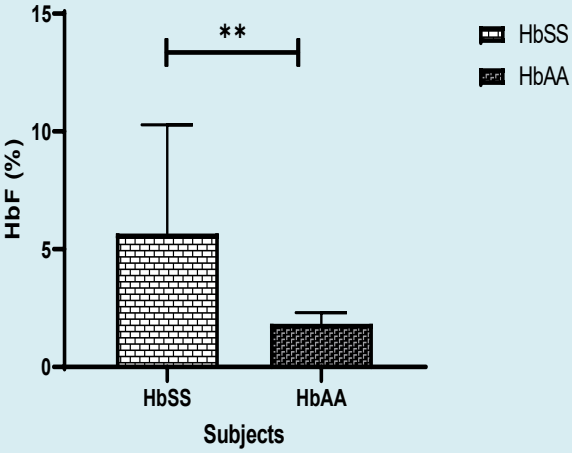

Figure (1a): Foetal haemoglobin concentration of the study population. ** P < 0.01

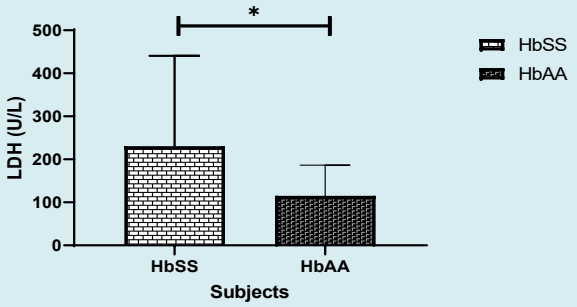

Figure (1b): Lactate dehydrogenase activity of the study population. * P < 0.05.

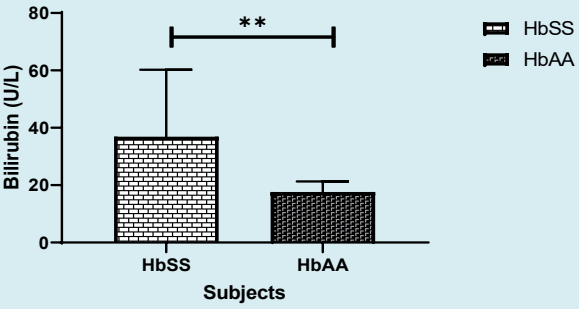

Figure (1c): Bilirubin concentration of the study population. ** P < 0.01

The subjects were classified based on foetal haemoglobin concentration (Figure 2a). Twenty-one (21) subjects had HbF<5%, Thirteen (13) between 5 and 10% while Six (6) had HbF>10%. The lactate dehydrogenase activity (Figure 2b) and bilirubin concentration (Figure 2c) of sickle cell subjects based on the foetal haemoglobin composition were also assayed. Subjects with HbF >10% both showed a significant reduction in the LDH and Bilirubin concentration compared to subjects with HbF<5%.

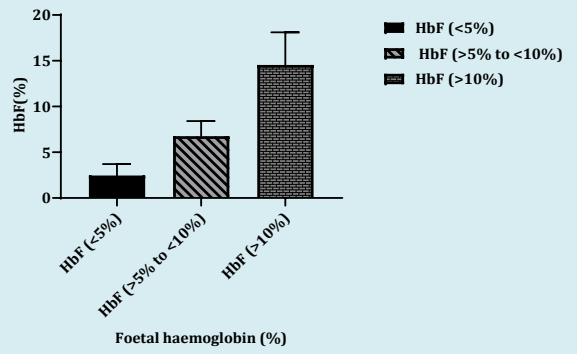

Figure 2a: Foetal haemoglobin classification of sickle cell subjects.

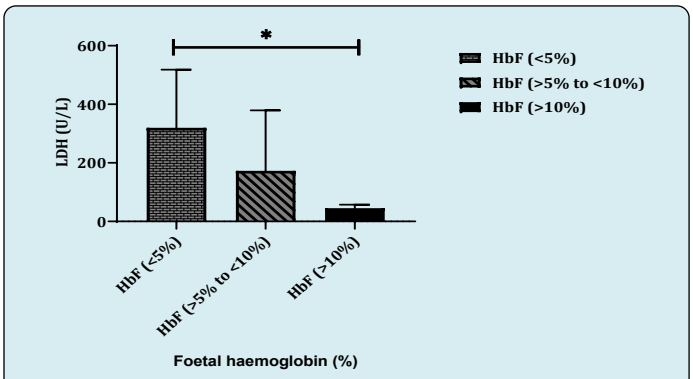

Figure 2b: Lactate dehydrogense activity classification of sickle cell subjects based on foetal haemoglobin concentration.

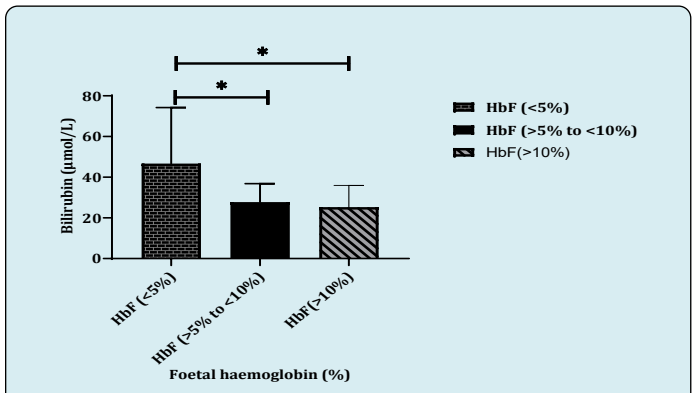

Figure 2c: Bilirubin concentration classification of sickle cell subjects based on foetal haemoglobin concentration

The correlation between foetal haemoglobin and the haemolysis markers, Lactate dehydrogenase (Figure 3a) and bilirubin (Figure 3b) was assayed. Foetal haemoglobin showed a significantly strong inverse correlation with both Lactate dehydrogenase activity and bilirubin concentration. On the other hand, lactate dehydrogenase showed a weak and direct correlation with bilirubin concentration (Figure 3c).

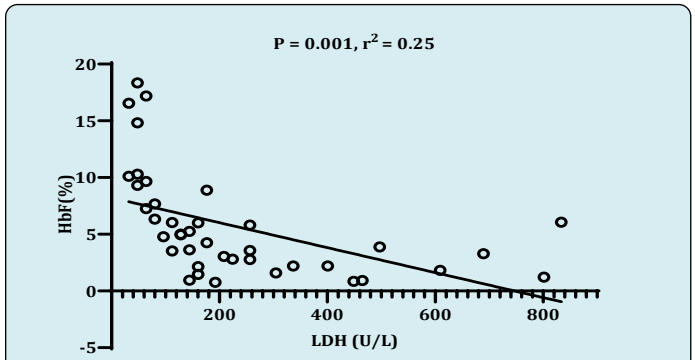

Figure 3a: Linear regression of foetal haemoglobin and Lactate dehydrogenase.

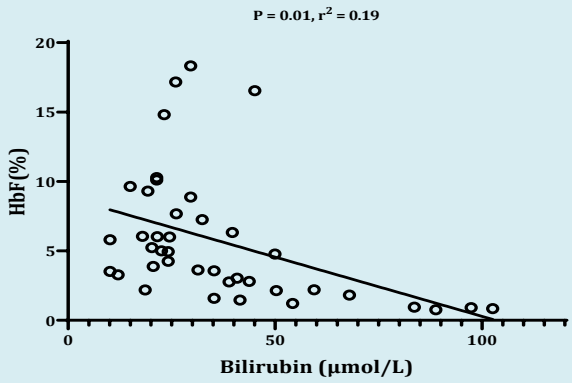

Figure 3b: Linear regression of foetal haemoglobin and Bilirubin concentration.

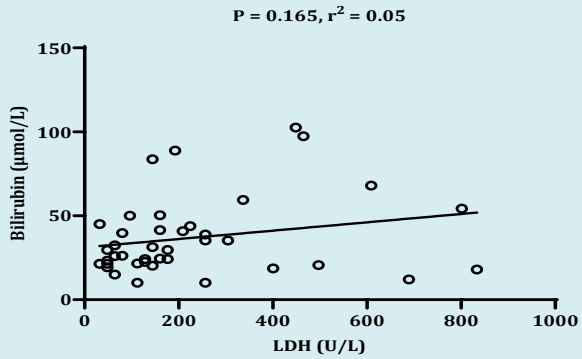

Figure 3a: Linear regression of bilirubin concentration and Lactate dehydrogenase activity.

Discussion

Foetal haemoglobin (HbF) is a well-established modifier of clinical outcomes of sickle cell disease. The synthesis of HbF is developmentally regulated, with higher amount synthesized at the infant stage [11]. The complications of sickle cell disease vary among subjects with sickle cell disease. While some experience an aggressive form of the disorder, others experience a less aggressive form of the disorder [12-14]. In this study, Lactate dehydrogenase and bilirubin were used to measure the level of disease severity in the subjects. Therefore, this study was focused on assessing the impact of HbF, on disease severity among subjects with sickle cell subjects.

Specialized red blood cells (F-cells), responsible for the synthesis of HbF are found in relatively high concentration in some adults with sickle cell diseases [15,16]. In the current study, the sickle cell subjects had a HbF of 5.76% which was also significantly higher than in the normal subjects. The sickle cell subjects were classified based on HbF concentration as; low (HbF<5%), moderately-low (HbF >5 to <10%) and high (>10%) concentration group. Twenty-one (21) subjects had a low HbF, thirteen (13) had moderately-low HbF, while six (6) had high HbF concentration. This finding suggest that about 85% the sickle cell subjects had low HbF concentration while 15% had a high HbF concentration. This finding aligns with previous studies who also reported an averagely low HbF concentration among the sickle cell subjects investigated [17-20].

Lactate dehydrogenase activity and bilirubin concentration were analysed to ascertain disease severity (Fig 2). Sickle cell subjects generally presented a significantly elevated LDH activity and bilirubin concentration compared to normal subjects. A further classification of the above markers based on HbF concentration revealed a significant reduction in the concentration of LDH and bilirubin among subjects with moderately-low HbF (mean=6.76%) and high HbF (mean= 14.54%) compared to those with low HbF (mean=2.46%). However, the difference between subjects with moderately-high HbF and High HbF concentration was not significant. This finding suggest the benefits of high concentration of HbF in neutralizing HbS polymerization, which is primarily responsible for sickle cell complications HbF [21,22]. Previous studies have also associated higher HbF concentration with less severe disease complications in sickle cell disease [23,24].

The biochemical relationship between HbF concentration with disease severity markers, LDH and bilirubin concentration (Figure 3) was assayed to determine the impact of HbF on disease severity. Our finding revealed a significant inverse correlation between HbF with LDH and bilirubin. This finding revealed a decrease in the concentration of the severity markers with increasing HbF concentration and vice versa with increase in concentration of the severity markers. This observation is in agreement with the studies of Pierre, et al. [25] and Nouraie, et al. [26] who also reported similar findings.

Conclusion

The foetal haemoglobin concentration of the study was low and demonstrated an inverse relationship with the severity markers (LDH and bilirubin). Subjects with higher foetal haemoglobin concentration presented lower levels of LDH and bilirubin concentration, while those with lower foetal haemoglobin concentration presented higher levels of LDH and bilirubin concentration. The findings of this study therefore, provides valuable insights into role of foetal haemoglobin concentration and its impact on disease severity among sickle cell subjects from Nigeria.

Competing Interest

The author declares that there is no conflict of interest

Funding

No funding was received for this study

Running title

Interplay of HbF and Haemolysis in SCD

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