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Serum Levels of Immunoglobulin M, Interleukin-10 and C-Reactive Protein in Adults with Sickle Cell Disorder in Nigerian Population

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ABSTRACT

Background: Evidence suggests that sickle cell disorder (SCD) is associated with a chronic inflammatory state. This study was aimed at evaluating the levels of inflammatory and immunological parameters (immunoglobulin (Ig) M, interleukin (IL)-10, and C-reactive protein (CRP)) in Nigerian patients with SCD and comparing them with those in age- and sex- matched healthy subjects.
Methods: A total of 90 participants were recruited into this study, 45 of whom were SCD subjects from the clinic of the Department of Haematology, University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt, while the other 45 were healthy subjects from the Blood Donor Centre of the same institution. Serum levels of IgM, IL-10 and CRP were assayed using commercial Enzyme Linked Immunosorbent Assay (ELISA) kits.
Results: The mean serum concentrations of IgM and CRP were statistically significantly ($p<0.05$) lower in the SCD subjects compared to the control subjects. On the other hand, IL-10 was statistically significantly ($p<0.05$) higher in the SCD group than the control subjects. Also, the levels of IgM, IL-10 and CRP were not different between the male and female groups as well as among the different age groups in both the SCD and control subjects.
Conclusion: The results suggest that inflammatory mediators may be altered and may play a role in the pathogenesis of sickle cell disorder.

Keywords: sickle cell disorder; immunoglobulin M; interleukin 10; C-reactive protein

INTRODUCTION

Sickle cell disorder (SCD) is a potentially devastating condition that is caused by an autosomal recessive inherited hemoglobinopathy which results in vaso-occlusive phenomenon and haemolysis.[1] The complications of the condition are widely variable, but overall mortality is increased and life expectancy decreased when compared to the general population. SCD first appeared on the western medical scene in 1910, as a strange disease which was described by Herrick as an unknown disorder.[2] The disorder was then known as a "black'' disorder until 1949 when the molecular nature of sickle cell was discovered. [3] In 1958, Ingram discovered the genetic basis of the disorder and demonstrated that it originated from the substitution of a valine for glutamic acid at the sixth amino acid position of the hemoglobin beta chain. [3] This amino acid substitution is now known to be the result of a single point mutation of the hemoglobin

gene, which produces profound changes in the behaviour and conformation of the hemoglobin molecule in individuals affected by the disorder. [4]

SCD is a global health problem affecting millions of people worldwide. The highest burden of SCD is in Africa, where an estimated 80% of the global burden of the disease is concentrated. [5] There are many types of SCD and the most common type includes sickle cell anaemia (HBSS), the sickle beta-thalassemia (HbSB0 and HbSB+), hemoglobin SC disease (HBSC), and SCD with hereditary persistence of fetal hemoglobin (S/HPFH).[6] It is associated with a range of acute and chronic complications, among which microvessel occlusion, commonly known as vaso-occlusive crisis (VOC), is the pathological process that has the most clinical significance. [7] Some clinical features include anaemia, severe pain, chest pain, pallor, strokes, joint pain, and severe infections. The most common causes of death in children and adults with SCD are infections, acute chest syndrome, and stroke.

It is becoming more widely recognized that SCD is an inflammatory condition linked to changes in immune phenotype and function. [8] Although splenic dysfunction—which is the result of an auto infarction that occurs in early childhood and causes functional asplenia—has historically been thought to be responsible for immune abnormalities in SCD, [9] there is increasing evidence that the immune deviation in SCD goes beyond splenic-associated abnormalities and that SCD is a pro-inflammatory condition with exaggerated immune activation. [10] Apart from the phenomenological findings that support immune activation in sickle cell disease (SCD), recent research has started to demonstrate that immune activation plays a role in the disease's pathophysiology.[8] Studies have shown that patients with SCD have higher levels of cytokine production, [11] as well as greater activation of neutrophils,[12] and monocytes.[13] This is especially true during vaso-occlusive crises. Additionally, there is evidence of increased activity and levels of invariant natural killer T cells, which have been linked to pulmonary ischemia-reperfusion injury in murine SCD,[14] and have been demonstrated to be elevated in SCD patients both at steady state and during vaso-occlusive crisis. [15]

Previous studies investigating the levels of immunological parameters such as immunoglobulins, pro-inflammatory and anti-inflammatory cytokines in SCD patients have reported contrasting findings with some reporting increased levels in SCD patients and others reporting no significant difference or decreased levels when compared to apparently healthy individuals. [16-19] Therefore, there is need to better understand the roles of these biomarkers in the pathophysiology of SCD and their clinical utility in the management of the disease.

This study was aimed at investigating the serum levels of immunological parameters such as Immunoglobulin M (IgM), Interleukin- 10 (IL-10) and C-reactive protein (CRP), as well as the socio-demographic pattern of adult Nigerian patients with SCD. IgM is a pentameric antibody consisting of five identical subunits, each composed of two heavy chains and two light chains, linked together by disulfide bonds. It has a key role in protecting the body from various bacterial, fungal, viral, and parasitic infections. [20] IL-10 is a versatile anti-inflammatory cytokine that is secreted by monocytes/macrophages, type 2 helper T cells (Th2), B cells, regulatory T cells (Treg), and dendritic cells. [21] It regulates the differentiation and activation of T and B cells, promoting the generation of regulatory T cells (Tregs) and suppressing the maturation of dendritic cells and the activation of effector T cells. CRP is a pentameric protein found in blood plasma and whose circulating concentrations rise in response to inflammation. [22] CRP serves as an early marker of inflammation or infection and is the principal downstream mediator of

the acute-phase response following an inflammatory event.

MATERIALS & METHODS

This was a descriptive cross-sectional study which was conducted from July to December, 2022. The study population consisted of adult patients with sickle cell disorder who attended the Day-care/Clinic of the Department of Haematology, University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt, Nigeria. The sickle cell patients with phenotype "SS" aged between 18 to 60 years were recruited into the "case" group, while adults who had no sickle cell disease with phenotype "AA" aged between 18 to 60 years were selected as controls from the Blood Donor Centre of the same institution. The study population was made up of 45 sickle cell patients and 45 healthy controls. Participants were excluded if they had clinical infection.

Socio-demographic data including age, sex, occupation, medical history and diagnosis for each patient enrolled into the study were obtained from the patients using a standard questionnaire or extracted from patient files.

Venous blood (5ml) was collected from each participant by an intern doctor using aseptic procedure. The blood samples were put into plain polypropylene tubes and allowed to settle at room temperature for 30 minutes before centrifuging for 5 minutes at 450 rpm. The resulting supernatants were transferred into sterile polypropylene tubes using Pasteur pipettes. The serum samples were then immediately stored at -20^{o}C at the laboratory of the Chemical Pathology Department, UPTH until analysis of IgM, IL-10 and CRP using enzyme-linked immunosorbent assay (ELISA) kits (Aviva Systems Biology, San Diego, CA).

STATISTICAL ANALYSIS

Statistical analysis was done by SPSS version 25.0 (IBM, Chicago, IL). Summary statistics of each variable were presented as mean ± SD and as the number of subjects (percentage) as appropriate. Continuous variables were analysed by independent student t-tests, while categorical variables were analysed by Chi-Square tests. The Analysis of Variance (ANOVA) was used to compare means between three groups and the Pearson's correlation coefficient was used to assess the correlation between continuous variables in the different groups. An observation was considered significant if the p value < 0.05.

RESULT

Majority of the sickle cell patients were female, within 18-29 years, students and had blood group O (Table 1). In addition, mean age of the sickle cell group was higher than that of the control group, however, there were no statistically significant differences in age, gender and distribution of blood group between the SCD and control groups.

Serum concentrations of IgM and CRP in the SCD subject were statistically significantly ($p<0.05$) lower than that of the control group (Table 2). On the other hand, serum concentration of IL-10 was statistically significantly ($p<0.05$) higher in the SCD group than in the control group. In addition, there were no differences in the serum concentrations of IgM, IL-10, and CRP when compared by gender and age in the SCD and control groups (Tables 3 and 4). Furthermore, a strong positive and statistically significant ($p<0.05$) correlation was observed between IgM and CRP in both the SCD and control groups (Figure 2a and b).

Table 1: Demographic data of SCD and healthy subjects.

Variables	SCD Patients (n=45)	Control group (n=45)	P value
Gender			
Male	18 (40)	18 (40)	1.0
Female	27 (60)	27 (60)	
Age Group (years)			
18-29	34 (75.6)	36 (80)	
30-39	8 (17.8)	5 (11.1)	0.64
40-49	3 (6.7)	4 (8.9)	

Mean Age (years)	26.7 ± 6.8	25.9 ± 7.1	0.554
Phenotype			
AA	0 (0)	45 (100)	
SS	45 (100)	0 (0)	
Blood group			
A	7 (15.6)	5 (11.1)	
B	3 (6.7)	8 (17.8)	0.05
AB	4 (8.9)	11 (24.4)	
O	31 (61.9)	21 (46.7)	
Occupation			
Student	31 (68.9)	15 (33.3)	
Employed	5 (11.1)	11 (24.4)	
Unemployed	3 (6.7)	2 (4.4)	
Business	6 (13.3)	17 (37.8)	

Values are presented as Mean ± SD for continuous variables.
Values are presented as number of subjects (percentage).

Table 2: Immunological parameters of healthy and SCD subjects

Parameters	SCD group	Control group	p value
IgM (mg/dl)	98.51 ± 33.11	143.73 ± 38.93*	0.003
IL-10 (pg/ml)	2.56 ± 1.35	1.84 ± 0.73*	0.000
CRP (mg/dl)	0.51 ± 0.17	0.72 ± 0.20*	0.000

Values are presented as Mean ± SD.
Data were analysed by independent student t-tests.
*Difference between SCD and control groups is statistically significant ($p < 0.05$).

Table 3: Comparison of Immune parameters by Gender

Variables	Male	Female	p value
IgM			
Sickle cell group	101.73 ± 39.10	96.36 ± 29.05	0.600
Control	132.52 ± 39.28	151 ± 37.59	0.116
IL-10			
Sickle Cell group	2.83 ± 1.61	2.37 ± 1.14	0.272
Control	1.78 ± 0.69	1.89 ± 0.76	0.224
CRP			
Sickle cell group	0.55 ± 0.21	0.48 ± 0.15	0.254
Control	0.69 ± 0.20	0.74 ± 0.20	0.391

Table 4: Comparison of Immune parameters by Age

Parameters	18 – 29 years (A)	30 – 39 years (B)	40 – 49 years (C)	ANOVA (p value)	Multiple Comparisons (p value)		
					A vs B	A vs C	B vs C
IgM							
SCD group	99.53 ± 34.67	95.44 ± 34.67	95.13 ± 2.46	0.939	0.760	0.830	0.989
Control group	142.96 ± 39.97	148.98 ± 30.94	144.13 ± 47.60	0.951	0.753	0.956	0.857
IL-10							
SCD group	2.72 ± 1.46	2.12 ± 0.79	1.91 ± 0.83	0.375	0.264	0.329	0.825
Control group	1.90 ± 0.76	1.81 ± 0.73	1.36 ± 0.13	0.369	0.795	0.161	0.356
CRP							
SCD group	0.52 ± 0.18	0.47 ± 0.18	0.48 ± 0.01	0.750	0.478	0.731	0.915
Control group	0.72 ± 0.20	0.72 ± 0.19	0.74 ± 0.25	0.976	0.998	0.828	0.866

All values are presented as Mean ± SD.
ANOVA, analysis of variance, was done to compare between the 3 groups; multiple comparisons between two groups were done with independent student t-test

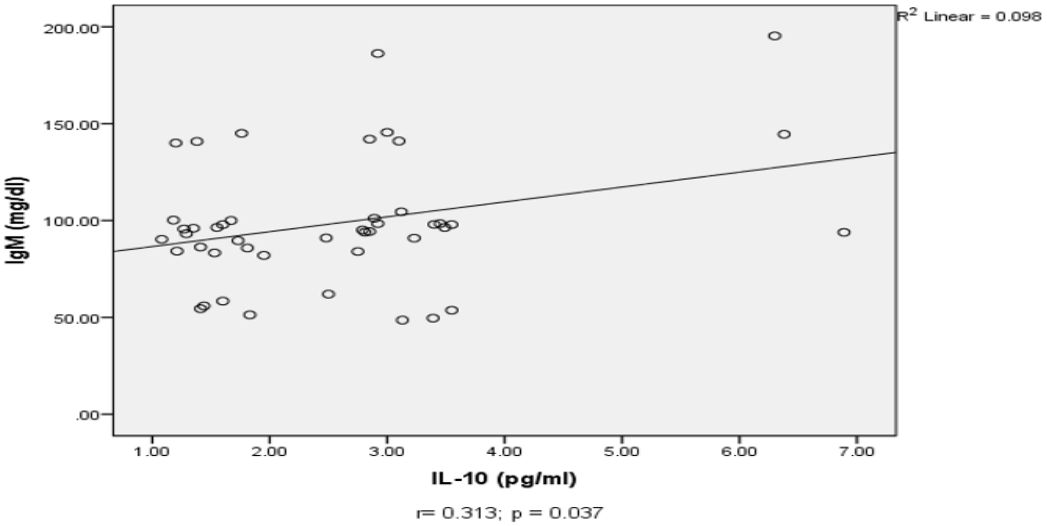

Figure 1a: Scatter plot for correlation between IgM and IL-10 in the SCD group

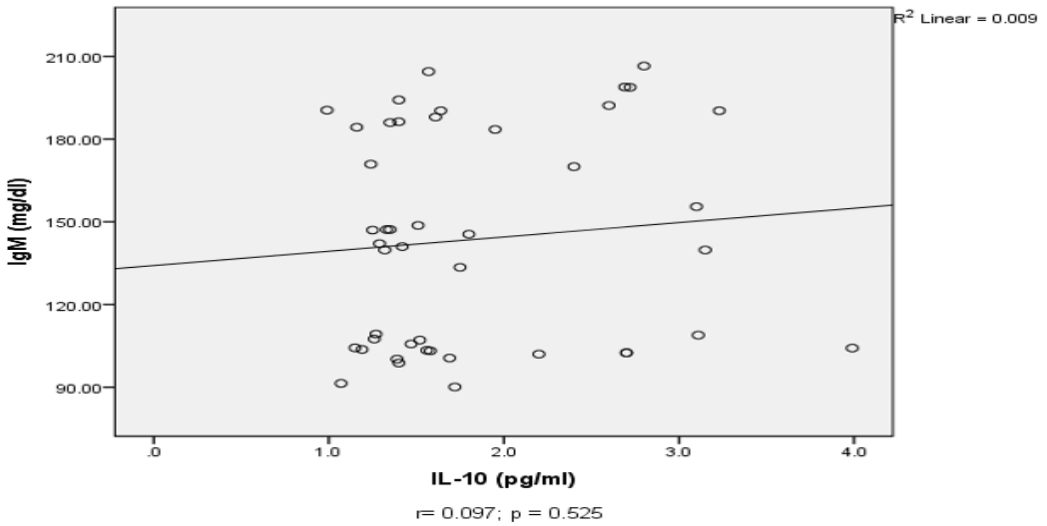

Figure 1b: Scatter plot for correlation between IgM and IL-10 in the Control group

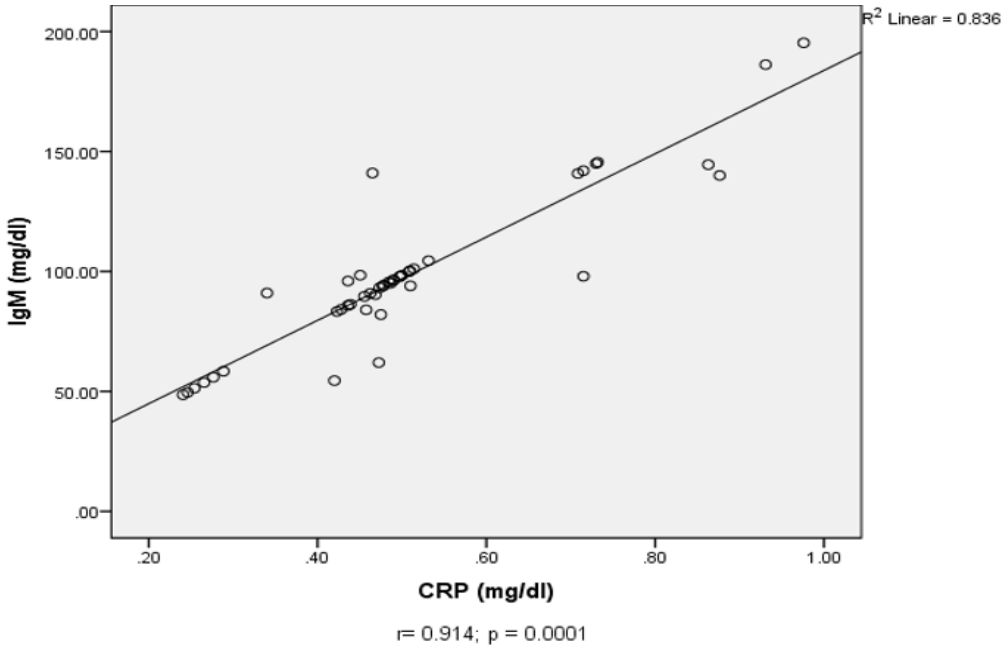

Figure 2a: Scatter plot for correlation between IgM and CRP in the SCD group

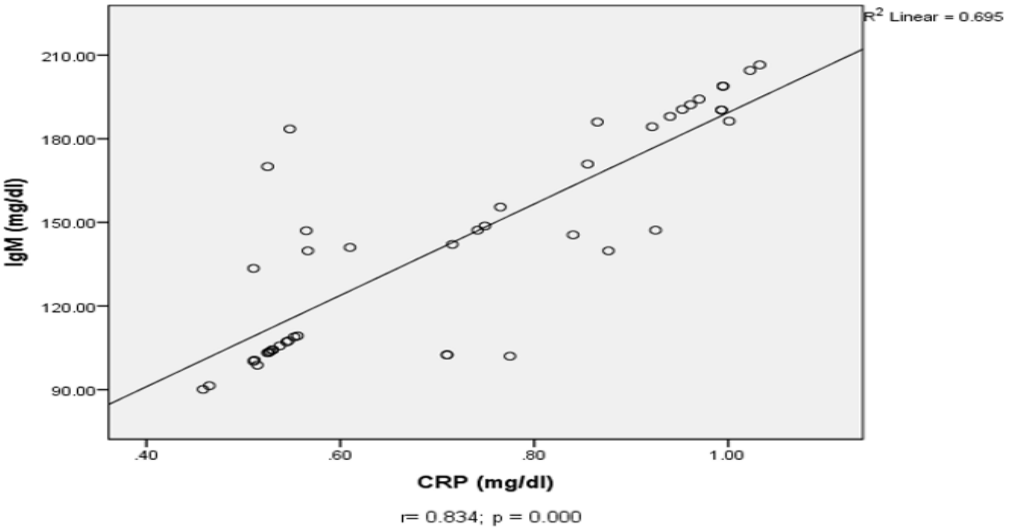

Figure 2b: Scatter plot for correlation between IgM and CRP in the control

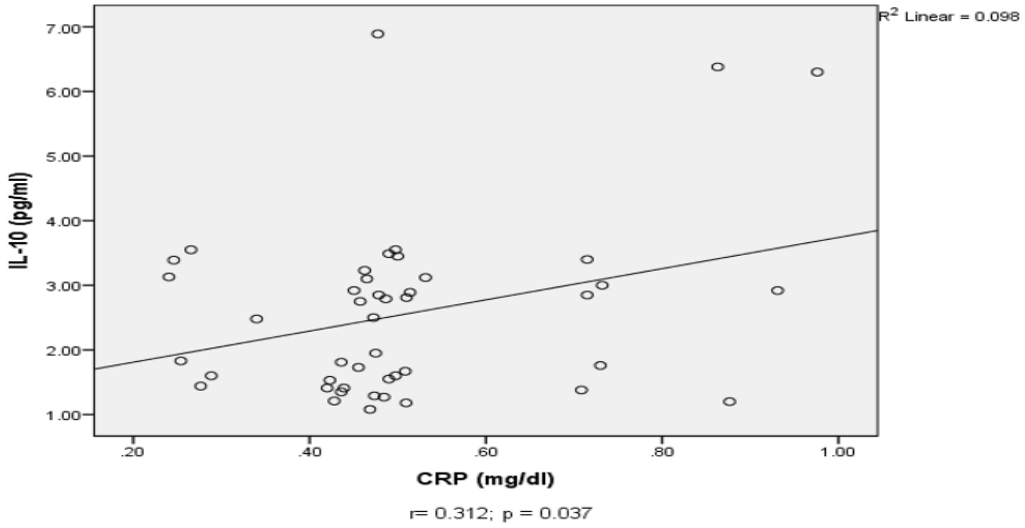

Figure 3a: Scatter plot for correlation between IL-10 and CRP in the SCD group

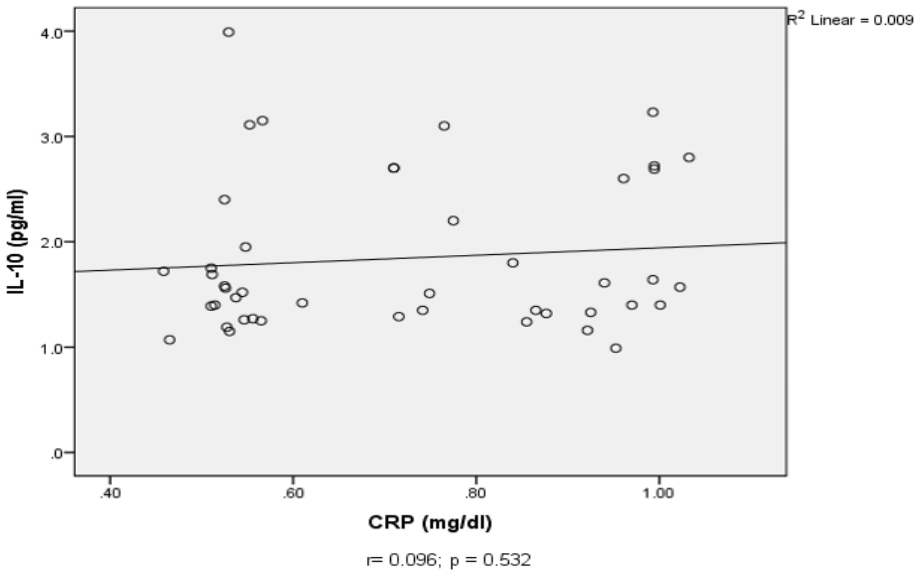

Figure 3b: Scatter plot for correlation between IL-10 and CRP in the Control group

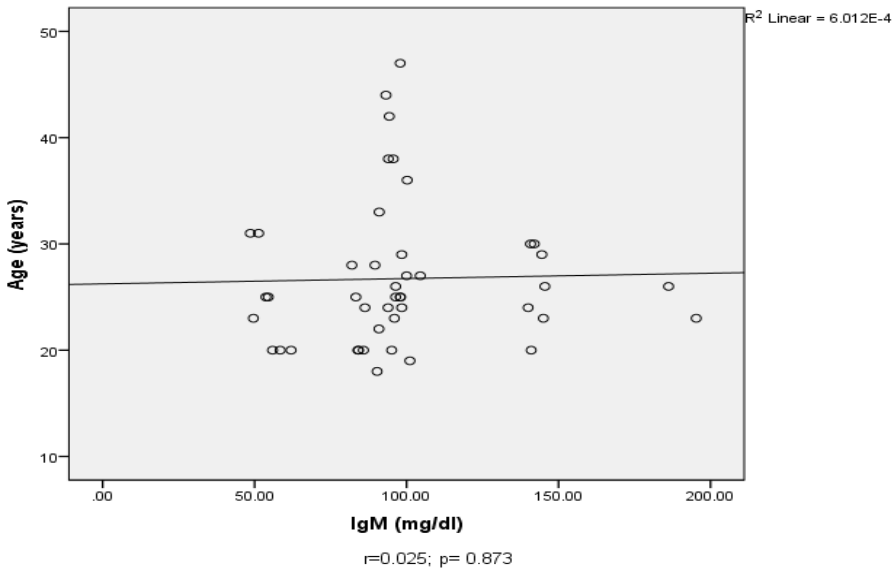

Figure 4a: Scatter plot for correlation between Age and IgM in the SCD group

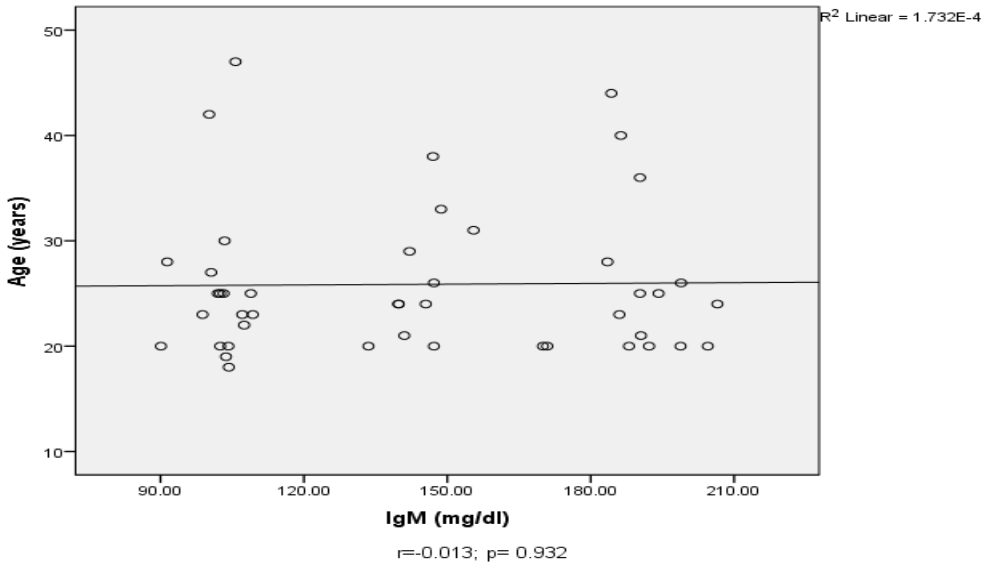

Figure 4b: Scatter plot for correlation between Age and IgM in the Control group

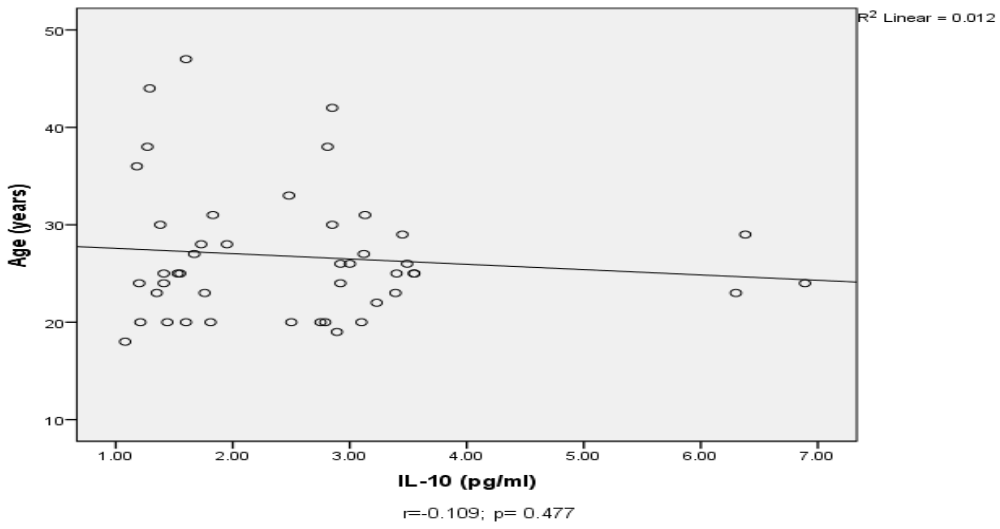

Figure 5a: Scatter plot for correlation between Age and IL-10 in the SCD group

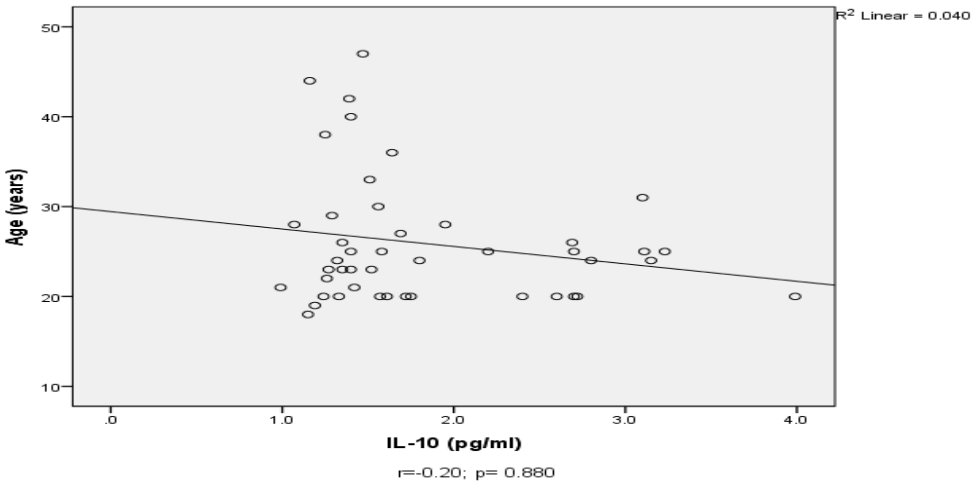

Figure 5b: Scatter plot for correlation between Age and IL-10 in the Control group

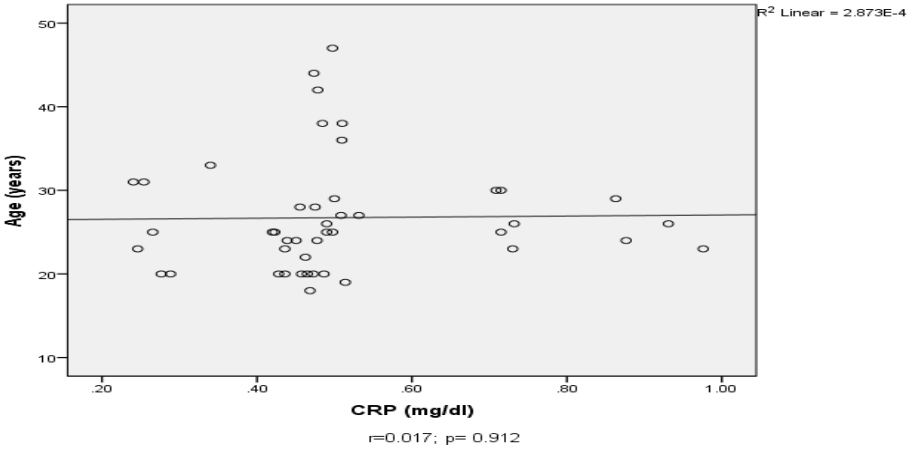

Figure 6a: Scatter plot for correlation between Age and CRP in the SCD group

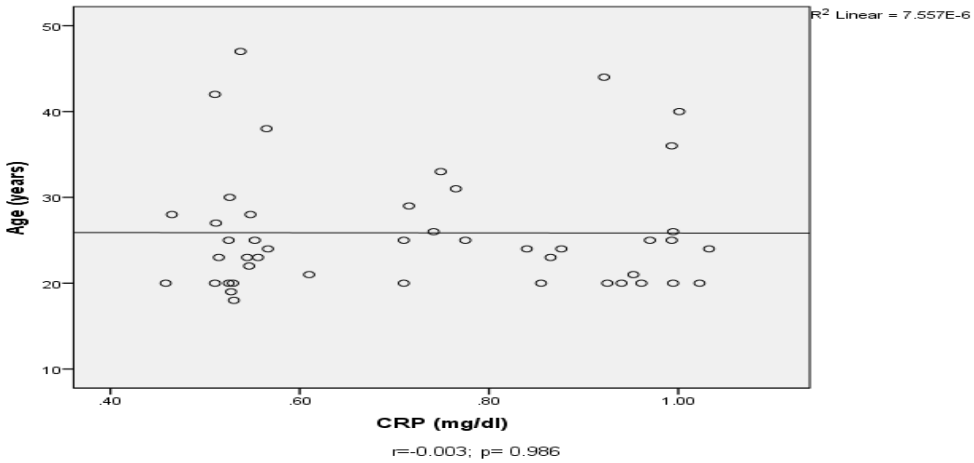

Figure 6b: Scatter plot for correlation between Age and CRP in the SCD group

DISCUSSION

This study evaluated the levels of immunological parameters in adult Nigerian patients with SCD and compared them with apparently healthy subjects. Regarding the socio-demographic pattern of adult Nigerian patients with SCD, this study showed that majority of the sickle cell patients were females, within 18-29 years, students and had blood group O. Also, mean age of the sickle cell subjects was 26.7 ± 6.8 years. This is consistent with previous studies conducted in Nigeria which reported that majority of the SCD samples were females

within the age group of 15-29 years and had a mean age of about 27 ± 5.5 years. [17,23] In addition, other studies have reported similar characteristics among their SCD subjects, however, with differences in the age group and marital status. For example, Levenson and colleagues [24] as well as Mclish et al [25] reported that the highest frequency of sickle cell disease was found among patients who were females, had high school education, were single and were between 25 and 34 years, while Amaral and colleagues observed that majority of their SCD subjects where patients who were females, married, between 30 and 39 years old and had attained high school education. [26]

The results of this study also demonstrated a significant reduction in the serum level of immunoglobulin M (IgM) in the SCD subjects compared to the control. Previous studies on the level of IgM among SCD patients have reported contrasting results. While some studies have reported low or normal levels of IgM among SCD patients,[27-29] others have reported higher levels compared to the controls.[17, 30-31] Generally, the studies which reported low or normal levels of IgM in SCD patients were conducted in non-tropical regions of the world, and in these studies, a correlation between loss of splenic tissue and low IgM concentration was suggested by the authors. On the other hand, the studies which reported higher levels of IgM compared to controls were conducted mainly in tropical regions of the world and this observation was largely attributed to environmental factors prevalent in the tropics, such as recurrent malaria infection. Indeed, malaria infection has been demonstrated to be a mitogen that can trigger the proliferation of B cells.[32] Also, a direct correlation between malaria antibody titre and serum antibody levels have been reported among Nigerian patients with SCD.[33] However, the results of this study did not appear to follow the above pattern as the study was conducted in the tropics and yet the serum level of IgM was significantly lower than that of the control group. Nevertheless, the finding of this study is consistent with that of Nnodim and colleagues who reported lower levels of IgM (although not significant) among Nigerian SCD patients in steady state as well as those undergoing vaso-occlusive crises compared to the control subjects.[34] It may be possible that the SCD patients recruited in this study had no underlying infection to trigger the production of IgM.

The results of this study, which showed a significantly higher serum level of IL-10 among SCD patients compared to the control group, is consistent with that of the study by Musa and colleagues, where patients in steady state had higher IL-10 levels than either patients in VOC or normal healthy controls.[35] It is also in agreement with studies by Veiga and colleagues which reported increased level of IL-10 in Brazilian children with SCD, who were of African descent origin.[36] The increase in level of IL-10 may be attributed to the triggering of a compensatory anti-inflammatory mechanism in a bid to downregulate the ongoing inflammatory state. However, this result is in contrast with other studies which showed that the level of IL-10 in SCD patients were comparable to those of healthy controls. [21,37]

This study also demonstrated that there was a significant reduction in the serum level of C-reactive protein (CRP) in the SCD group compared to the control group. This is however in contrast with previous studies which have reported increased serum levels of acute phase proteins during the steady state of SCD.[24-25] Specifically, some studies have shown that the level of C-reactive protein was higher at steady state and to even rise further in acute vaso-occlusive crisis.[11,39] This has been suggested to be due to the subclinical microvascular occlusions in steady state and the resultant local tissue ischemia.[39] These subclinical microinfarctions are thought to be triggered by the increased adhesiveness of reticulocytes and irreversibly sickled erythrocytes to the vascular endothelium, resulting in persistent endothelial activation and damage and the generation of

inflammatory cytokines (such as IL-1, IL-6, IL-8, and TNF-α) by the activated endothelial cells.[11] These cytokines increase the ability of red blood cells to adhere to endothelium, triggering a vicious loop that causes an accumulation of denser, permanently sickled erythrocytes, platelets, and neutrophils, and eventually resulting in clinical microvascular occlusion, also known as VOC.[40] As sickle cell disease is thought to be associated with chronic inflammation, it is not clear why the level of CRP in this study is reduced in the SCD group compared to the controls. However, the discrepancy between the results of this study and previous studies regarding the level of CRP warrants further studies, maybe utilizing a larger sample size.

This study also showed that the concentrations of IgM, IL-10 and CRP were comparable between the males and females in both the SCD and control groups. While studies assessing the levels of IgM, IL-10 and CRP among sickle cell patients by gender could not be found, previous studies conducted on healthy population have similarly reported comparable IgM and IL-10 levels between males and females.[41-42] In contrast, some studies have reported higher CRP levels among females than males while others have reported higher levels in males than females.[43-44] Furthermore, this study demonstrated that the levels of IgM, IL-10 and CRP in the SCD subject were not different from those of the control for all age groups. In line with this, no significant correlation was observed between age and the measured immune parameters in both the SCD and control groups in this study. Previous studies assessing the levels of CRP and IL-10 among sickle cell patients by age groups could also not be found. However, this result is somewhat similar to a study conducted among children which reported no differences in IgM levels between severe sickle genotypes and milder genotype from early childhood to late adolescence, even though low IgM levels were observed over time.[28] In addition, a positive and significant correlation was observed in this study between IgM and IL-10, IgM and CRP, as well as IL-10 and CRP in the SCD group. These may be attributed to compensatory mechanisms associated with the ongoing inflammatory state.

CONCLUSION

This study has shown low levels of IgM and CRP as well as high levels of IL-10 among patients with sickle cell disease in Port Harcourt, Nigeria and suggests that inflammatory mediators may be altered in sickle cell disease and may be involved in the pathogenesis of the disease.

Declaration by Authors

Ethical Approval: This study was approved by the Research Ethics Committee of the University of Port Harcourt, Nigeria (UPH/CEREMAD/REC/MM65/016). The research was also carried out in line with the Helsinki Declaration.

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Conflict of Interest: The authors declare no conflict of interest.

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