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Serum levels of antiphospholipid antibodies among patients with sickle cell anaemia in Zaira Nigeria

***Medlyn Chimaluoke Okolo*[*1], *BabadokoA.A*[2], *Umar A*[3], *Wada Rabiu Yunusa*[4]**

1- Departments of Public Health, National Open University of Nigeria, Abuja,

2- Department of Haematology, Ahmadu Bello University/Teaching Hospital, Zaria Nigeria,

3- Department of Medicine Immunology Unit, Ahmadu Bello University, Zaria Nigeria,

4- School of Nursing, Ahmadu Bello University Teaching Hospital, Zaria Nigeria, Department of Medical Laboratory Science, Ahmadu Bello University/Teaching Hospital, Zaria Nigeria

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ABSTRACT

Background: Antiphospholipid (APL) antibody is rarely reported in patients with sickle cell anaemia (SCA). It is an autoimmune response to phospholipid in which negatively charged phospholipids translocate from the inner to the outer surface of red blood cell (RBC) membranes, leading to the potential generation of an antigenic target in patients SCA following recurrent Vaso-occlusive episodes. Subsequent induction of APL antibody is characterized by recurrent fetal loss, arterial or venous thrombosis and thrombocytopenia with a mortality rate of 50%, due to multi-organ dysfunction. This study aimed to determine the prevalence of both Anticardiolipin (aCL) and β2 glycoprotein 1(β_2GP1) IgM and IgG antibodies among adult patients with SCA in Ahmadu Bello University Teaching Hospital Zaria (ABUTH), Nigeria. **Methods:** A comparative cross-sectional study of patients with SCA (HbSS) as Study group and prospective blood donors (HbAA) as control, of ages 18years and above. Ethical approval was obtained and a total of 118 participants were enrolled after an informed consent; 79 HbSS and 39 HbAA. Haematological parameters were determined by multiparameter analyzer Swelab alfa while Serum levels of Anti cardiolipin (aCL) antibody and β2 glycoprotein 1 (β2GPI) IgM/IgG were evaluated using ELISA technique, Sunlong Biotec LTD (SL12654Hu). Data was analyzed using SPSS version 23 and level of significance was set at $p \leq 0.05$. **Results:** Out of the total number of SCA subjects studied 59.5% (47/79) were females while males constitute 89.7% (35/39) of the control. The median age of the study group (HbSS) and controls (HbAA) were 22 and 28 years respectively**.** The median haemoglobin concentration of the SCA subjects 7.70g/dl (1.90) was significantly lower than that of the control group 13.80g/dl (1.70), $p < 0.0001$. The Median (IQR) of aCL IgG/M and β2GP1 IgG/M of the study group were; 48(16.00)u/ml, 22(9.00)u/ml and 548(100.00)ug/L, 113(88.00)ug/L respectively and were significantly higher when compared with that of the control group aCL IgG/M and β2GP1 IgG/M; 41(5.00)U/ml, 16(6,00)U/ml and 521(42.00)ug/L, 54(48.00)ug/L) respectively ($p<0.0001$). The prevalence of aCL antibodies was 2.5% IgG and 5.1% IgM while 5.3% IgG and 3.8% IgM for ß2-GP1. **Conclusion:** The elevated levels

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* *Corresponding author:* Medlyn Chimaluoke Okolo

E-mail address: obiezemedlyn@gmail.com

of APL antibody in patients with SCA may serve as a tool for the monitoring and surveillance of disease severity and thus a treatment and prognostic index for the improvement of the quality of care of these patients

Introduction

The World Health Organization (WHO) published global prevalence map of Sickle cell disease (SCD) and other data, estimate that about 20–25 million individuals worldwide have homozygous SCD [1]; 12–15 million in sub-Saharan Africa, the highest gene frequency is in tropical Africa [1,2], 5–10 million in India and about 3 million distributed in different parts of the world [3]. Nigeria bears the highest burden of SCD in the world with about 2 to 3% of the population being homozygous [4]. WHO reiterated that the prevalence of Sickle cell anaemia (SCA) is about 20 per 1000 births, this means that, about 150,000 children are born annually with SCA in Nigeria [1]. It is now reported that over 94% of those born with SCD now survive into adulthood in the US, France and UK in contrast to the high mortality in sub-Sahara Africa where 50–90% may die in the first five years of life [5]. Sickle cell disease poses a huge burden on the affected individuals and their families [1]. Despite harboring the highest population of SCD, in Nigeria families of patients with SCD bear most of the burden of care with attendant economic and psychological effects due to lack of national social welfare provisions [6].

The protean clinical manifestation of SCA is due mainly to repeated vaso-occlusion, chronic intravascular haemolysis, microvascular ischaemia and organ damage [7]. Antiphospholipid (aPL) antibody has been occasionally reported in patients with SCA. It results from a systemic autoimmune response to phospholipid due to repeated sickling which produces a structural disruption and rearrangement of red cell membrane in SCA [8,9]. Recurrent vaso-occlusion and subsequent exposure of negatively charged phosphatidyl serine, a membrane phospholipid that is normally confined to the inner leaflet of RBC membranes, is expressed on the outer membrane of RBCs has been implicated in the induction of antibodies (APL antibody) against these cell membrane constituents and consequently development of Antiphospholipid antibody syndrome (APS) [9]. It is characterized by recurrent fetal loss, arterial occlusive events such as stroke and myocardial infarction or venous thrombosis (5-fold increase), thrombocytopenia and neurological complications [7]. The mortality rate is 50% and death is due to multiorgan dysfunction [10,11]. Antiphospholipid antibodies have been detected in all age groups and the incidence increases with age [10,11].

The prevalence of APS is not known however, the estimated prevalence of aPL antibodies in the general population is 2%–5% [12]. Antiphospholipid antibodies may be found in up to 2% of apparently normal adults, only about 0.2% have high titre [13]. A study in Benin reported the prevalence of lupus anticoagulant (LA) in 11.4% of the patients with adult homozygous SCD [14].

Thus, both SCA and APS are associated with prothrombotic state, therefore, there is need for early detection of APS using Laboratory parameters such as Cardiolipin (CL) antibody and βeta 2-glycoprotein 1(β2-GP1) antibody in patients with SCA and institution of early and appropriate specific therapy for APS including targeted therapies (Belimumab and Sirolimus). The aim of this study is to establish the serum levels of anticardiolipin and β2glycoprotein 1 antibodies among adult patients with SCA attending ABUTH, Zaria Nigeria.

Materials and Methods

The study was a comparative Cross-sectional study, approved by the Ethical and Scientific Committee of Ahmadu Bello University, Zaria, Nigeria. The research subjects were adult Nigerians of both genders who volunteered and provided written informed consent. Study subjects with electrophoretic documentation of SS phenotype were consecutively recruited from the haematology clinic in 2021. Exclusion criteria included subjects unable to understand the investigational nature of the study or to give informed consent, those below the age of 18 years and those who had recent blood transfusion in the preceding three months. The control group included apparently healthy adults prospective blood donors with electrophoretic documentation of haemoglobin AA (non-sickle cell anaemia subjects) or AS phenotype. Subjects underwent complete history

and physical examination and laboratory investigations.

Blood Sample Collection

Six milliliters (6mls) of venous blood sample were collected from each participant. Three millimeters (3ml) of the blood was dispensed into a plain sample bottle and allowed to stand for 30 minutes to clot at room temperature. This was then centrifuged at 3000 rpm for 10 min to separate the serum from the cells. The serum was drawn into another plain sample bottle and stored at −20°C, before being analyzed with the enzyme-linked immunosorbent assay (ELISA) kits Sunlong Biotec LTD for IgM/IgG aCL and β_2-GP1. The microtitre plate reader was be used to read the results at a wavelength of 405 nm and only those with medium to high titer units were selected as positive.

The manufacturer's recommended cut-off values were used upon confirmation. The assay ranges are as follows [15].

Anti-Cardiolipin IgG (U/mL): Normal< 150, Elevated ≥150.

Anti-Cardiolipin IgM (U/mL): Normal< 65, Elevated ≥65.

Anti–*β*2glycoprotein 1 IgG (µg/L): Normal < 900, Elevated ≥900.

Anti–*β*2glycoprotein 1 IgM (µg/L): Normal < 500, Elevated ≥500.

The remaining 3mL of blood was be dispensed into an EDTA bottle for determination of Haematological parameters using Swelab alfa multiparameter analyzer .

Data Management/Statistical Analysis

The data was analyzed using IBM SPSS Statistics *version* 23 software. The quantitative variables were summarized using mean and standard deviation and/or median, (IQR) and ranges as appropriate. Qualitative variables were presented as frequencies and percentages. Level of significance was set at p≤0.05 with 90% confidence interval.

Results

A total of one hundred and eighteen (118) participants were evaluated comprising 79 subjects with SCA and 39 blood donors.

Socio-demographic characteristics of the study participants and controls

The median IQR (interquartile) age of the study and control groups was 22.00 (19.0, 30.0) and 28.00 (25, 35) respectively. Most of the 79 adults with SCA were females 59.5% (47) and 40.5% (32) males while out of 39 controls majority 89.7% (35) were males and only 10.3% (4) females.

Table l: Haematological parameters of the study participants

The Haemoglobin Concentration is significantly higher in the control group p <0.0001 when compared with that of the study group however, the total WBC and platelet counts are significantly higher in the study group p <0.0001.

Haematological Parameter	**Study group (n=79) Median (IQR)**	**Control group (n=39) Median (IQR)**	**P-value $^{\pi}$**
Haemoglobin Conc. g/dl	7.70(1.90)	13.80(1.70)	<0.0001
Total WBC (x10^3/µL)	13.07 ±8.31	4.86 ±1.23	<0.0001$^{\alpha}$
Neutrophils (x10^3/µL)	59.30(10.30	50.10(7.80)	<0.0001
Lymphocytes (x103/µL)	32.50(11.00)	40.10(5.40)	<0.0001
Monocytes (x103/µL)	4.00(1.90)	4.00(2.80)	0.839
Eosinophils (x103/µL)	2.1(2.80)	4.00(6.70)	0.011
Basophils (x103/µL)	0.90(0.60)	0.60(0.50)	0.002
Platelets (103/µL)	478.35 ±177.28	219.59 ±59.70	<0.0001α

Table Ii. Serum levels of Antiphospholipid antibodies among the study participants

The IgM and IgG levels of both anti-Cardiolipin and *β*2-glycoprotein 1 antibodies are significantly higher in the study group than in the control group p <0.0001.

Antiphospholipid antibody		**Study group (n=79) Median (IQR)**	**Control group (n=39) Median (IQR)**	**P-value [π]**
aCL (U/mL)	IgM	22.00 (9.00)	16.00 (6.00)	<0.0001
	IgG	48.00 (16.00)	41.00 (5.00)	<0.0001
ß2-GP1 (µg/L)	IgM	113.00 (88.00)	54.00 (48.00)	<0.0001
	IgG	548.00 (100.00)	521.00 (42.00)	0.008

[α]Mann-Whitney U test, t= test statistic, Median (Interquartile range)

Table III. Distribution of Antiphospholipid antibodies among the study participants

The prevalence of aCL among the study subjects, was 5.1% for IgG, and 2.5% for IgM respectively, while the prevalence ß$_2$-GP1 antibodies was 6.3% for IgG and 3.8% IgM respectively. However, among the control group, their parameters were found to occur in normal concentration.

Antiphospholipid antibody		**Study group (n=79)**	**Control group (n=39)**
aCL (U/mL)		**Frequency (%)**	**Frequency (%)**
IgM	Normal	77(97.5)	39(100)
	High	2(**2.5**)	0(0)
IgG	Normal	75(94.9)	39(100)
	High	4(**5.1**)	0(0)
ß2-GP1 (µg/L)			
IgM	Normal	76(96.2)	39(100)
	High	3(**3.8**)	0(0)
IgG	Normal	74(93.7)	39(100)
	High	5(**6.3**)	0(0)

Table IV. Gender Distribution of Antiphospholipid antibody among the study group

The prevalence of both IgM (2.8%) and IgG (4.3%) aCL antibody and IgG (6.4%) β2-GP1 was higher in the female study subjects than that of the males (IgM 1.4% and IgG 2.1% aCL antibody) and β2-GP1 IgG 6.4%, however these were not significant p > 0.05.

Antiphospholipid antibody		**Study group**		**P value***
aCL (U/mL)	**Level**	**Frequency (%)**		
		Male (n=)	**Female (n=)**	
IgM	Normal	70(98.6)	46(97.9)	0.999
	High	1(**1.4**)	1(**2.1**)	

IgG	Normal	69(97.2)	45(95.7)	0.999
	High	2(**2.8**)	2(**4.3**)	
β2-GP1 (µg/L) IgM	**Level** Low	4(5.6)	0(0)	0.276
	Normal	65(91.5)	46(97.9)	
	High	2(**2.8**)	1(**2.1**)	
IgG	Normal	69(97.2)	44(93.6)	0.386
	High	2(**2.8**)	3(**6.4**)	

* Fisher's exact test

Table V. Age distribution of 1 Antiphospholipid antibody among the study group

The levels of both aCLand β2-GP1 IgM/IgG antibodies were elevated in the study group of less than 20years of age but lower in those above the age of 20 years, however these were not significant p > 0.05.

Antiphospholipid antibody		**Study group**		**P value***
aCL (U/mL) IgM	**Level**	**Frequency (%)** **≤20 years (n= 28)**	**>20 years (n= 51)**	
	Normal	27(96.4)	50(98.0)	0.999
	High	1(**3.6**)	1(**2.0**)	
IgG	Normal	26(92.9)	49(96.1)	0.612
	High	2(**7.1**)	2(**3.9**)	
β2-GP1 (µg/L) IgM	**Level** Normal	26(92.9)	50(98.0)	0.285
	High	2(**7.1**)	1(**2.0**)	
IgG	Normal	25(89.3)	49(96.1)	0.340
	High	3(**10.7**)	2(**3.9**)	

* Fisher's exact test

Recommended cut-off values used upon confirmation:

ACA IgM (U/mL): Normal< 65, Elevated ≥65

ACA IgG (U/mL) : Normal< 150, Elevated ≥150

ß2-GP1 IgM (µg/L): Normal < 500, Elevated ≥500

ß2-GP1 IgG (µg/L): Normal < 900, Elevated ≥900.

Table VI. Correlation of Anti-Cardiolipin antibody with Haematological parameters among the study participants

The correlation between IgM and IgG Anti-Cardiolipin antibody and Haematological parameters showed no significant linear relationship with all the parameters studied

Haematological Parameter	**Anti-Cardiolipin antibody**							
	Serum IgM				**Serum IgG**			
	Study group		**Control group**		**Study group**		**Control group**	
	r	**P- value**	**R**	**P- value**	**r**	**P- value**	**r**	**P- value**
Haemoglobin Conc. g/dl	0.092	0.419	-0.011	0.947	0.133	0.244	-0.089	0.591
Total WBC (x 10^3/µL)	-0.089	0.438	0.116	0.481	-0.269	0.017	0.043	0.795
Neutrophils (x 10^3/µL)	0.067	0.556	0.113	0.492	0.141	0.215	0.139	0.400
Lymphocytes x 10^3/µL	-0.105	0.357	**-0.332**	0.039	-0.156	0.169	-0.214	0.191
Monocytes (x 10^3/µL)	0.186	0.101	0.184	0.262	0.096	0.402	0.041	0.803
Eosinophils (x 10^3/µL)	0.151	0.183	0.213	0.194	0.144	0.204	0.141	0.393
Basophils (x 10^3/µL)	-0.053	0.644	0.155	0.347	-0.017	0.884	0.023	0.890
Platelets (x 10^3/µL)	0.086	0.451	0.174	0.291	-0.013	0.912	0.070	0.673

r = Spearman's rank correlation

Table VII. Correlation of ßeta 2-GP1 antibody with Haematological parameters among the study participants

The correlation between IgM and IgG ßeta 2-GP1 antibody and Haematological parameters showed no significant linear relationship with all the parameters studied

Haematological Parameter	***Beta* 2-glycoprotein 1 antibody**							
	Serum IgM				**Serum IgG**			
	Study group		**Control group**		**Study group**		**Control group**	
	r	**P- value**	**R**	**P- value**	**r**	**P- value**	**r**	**P- value**
Haemoglobin Conc. g/dl	0.130	0.254	0.004	0.979	0.068	0.554	0.047	0.778
Total WBC (x 10^3/µL)	-0.145	0.204	-0.013	0.937	-0.047	0.682	-0.105	0.523
Neutrophils (x 10^3/µL)	0.052	0.652	0.118	0.476	-0.039	0.735	0.195	0.234
Lymphocytes x 10^3/µL	-0.095	0.406	-0.360	0.024	0.032	0.781	0.050	0.761
Monocytes (x 10^3/µL)	0.201	0.075	0.182	0.267	0.080	0.486	0.043	0.794
Eosinophils (x 10^3/µL)	0.207	0.067	0.217	0.184	**0.251**	0.026	**-0.354**	0.027
Basophils (x 10^3/µL)	-0.010	0.932	0.042	0.799	-0.090	0.428	0.218	0.181
Platelets (x 10^3/µL)	0.138	0.224	0.042	0.798	0.127	0.263	-0.107	0.516

r = Spearman's rank correlation

Discussion

In this study, a cross sectional comparison of the serum levels of APL antibodies in patients with SCA and healthy individuals showed that the median ages of the study group (22 years) is representative of the general population of individuals with SCD [16] and comparatively similar to the age of the healthy subjects (28 years). These ages also fulfil the criteria of the testing APL antibodies as recommended by the Scientific and Standardization subcommittee of international Society of Thrombosis and Haemostasis (SSC-ISTH) [17]. It indicates that testing should be carried out on patient less than 50yrs of age. This is because an elevated prevalence of APL antibody is often seen with aging especially in centenarians without any clinical symptoms of APS [17]. Our study showed an elevated aCl and β2-GP1 in patients with SCD of less than and lower in those above the age of 20 years, it also revealed a higher prevalence in the female gender however we did not observe significant differences in aPL levels by age or gender. This is similar to the study by Claudia Rodriguez Rivera et al in 2022 in USA [18].

In this study, the significantly lower haematocrit levels in patients with SCA compared to the controls (Hb AA) is similar to previous reports and this has been associated to the chronic haemolysis and high susceptibility to infections in these patients [19,20]. Expectedly the significantly high white cell count in patients with SCA buttress earlier findings and this may be due to chronic pain resulting in the redistribution of leucocytes between the marginal and circulating pools of leucocytes [19,20,21]. The differential monocyte count was not statistically different between the study and control groups. This is in agreement with the findings of Rana G et al., in 2019 [22] reported in a study conducted in the Saudi Arabia involving fifty-two Saudi Arabia male and female sickle cell and sickle cell trait. Thus, monocytes may not be a relevant marker for sickle cell anaemia prognosis.

We also observed a significantly higher platelet count in patients with SCA than the controls, as is the expected finding in most asymptomatic patients with SCD [20] except in crisis situation such as vaso-occlusive crisis [23]. However, this is contradictory to the findings of Salawu *et al* [12], who reported lower but statistically non-significant mean platelet counts in asymptomatic patients with SCD. Minor episodes of microvascular occlusion do occur in the so called asymptomatic steady state but may be insufficient to cause the overt painful crisis, thus consuming some platelets [24].

Association of ß2-GP1 IgM with full blood counts among the study group and controls shows a significant weak negative relationship between lymphocytes count among the control group.

This clearly shows that antigens of infectious agents and host tissues might trigger an immune response. However, this is close to the findings of Durcan *et al.,* (2017) in US who reported 3% of β2 glycoprotein I can be found in healthy people [25] According to Cervera *et al.,.(*2004) on their study reported urinary tract infections constituted the most common infections found as triggering factors in the most recent review of antiphospholipid antibody [26]. Relationship of ß2-GP1 IgG with full blood counts shows a significant weak positive relationship with Eosinophils in the study group. This is in line with Canali et al who reported that elevated eosinophil counts may be significantly seen in SCA individuals especially when cells are in an activated state [27]. Eosinophils which are very important for the control parasitic infections, are also involved in vital defensive tasks against bacterial and viral pathogens through the release of coarse granules that can be show toxic to host tissues and dysregulate heamostasis [28]. Immunoglobulin M β2GP1 may be the most sensitive assay to determine the presence of antiphospholipid in those with sickle cell anaemia especially in blacks of Northern Nigeria as IgM β2GP1 was the most elevated immunoglobulin in both HbSS and HbAA in this study. The prevalence of APLA of both the ACA IgG/M and β2GP1 IgG/M in this study is 2%-5% which is similar with the work done in Lagos, Nigeria by Olayimka *et al.,* on 113 SCA patients who reported 8% prevalence of APLA [29]. The estimated prevalence of antiphospholipid antibodies (aPL) in the general population is 2%–5% [12]. Antiphospholipid antibodies may be found in up to 2% of apparently normal adults, only about 0.2% have high titres [13]. Like other autoantibodies, prevalence increases with age [10].[10]

The mean values for ACA IgG/M and β2GP1 IgG/M estimated in this study group (HbSS) were (48U/mL, 22U/mL and 548ug/L, 113ug/L respectively) significantly higher than the mean values compared with the control group (Donors with HbAA), where ACA IgG/M and β2GP1 IgG/M were 41u/ml, 16u/ml and 521ug/L, 54ug/L respectively. This mean values on IgG ACA in this study is higher than that obtained from a study carried out in Slovenia [30] Europe which reported mean values of ACA IgG of 13.5u/ml in the study group and 14.4u/ml IgG in the control group and also higher than the study done by Rolla et al [31]. This difference can be attributed to the study being

done among children, and this may be a consideration that APLA like other autoimmune antibodies increase with age [29]. However immunoglobulin IgM ACA both in the study group and control group (22U/ml and16U/ml) respectively were lower than APLA obtained in Slovenia Europe (36.9U/ml and 42.6U/ml) in both study and control group respectively [30]. These variations could also be due to differences in the specificity and sensitivity of the assay used. Immunoglobulin IgG B2GP 1 serum level in this study were insignificant both in the study and control groups. These observations are likely due to recurrent, epidemiological or demographical characteristics that result in different rates of exposure to autoimmune, drugs or infection. The elevated serum immunoglobulin IgM β2GP1 level that was most abundant in both study and control group shows recent reaction, because IgM antibodies is the first antibodies produced during humoral immune response and later substituted by IgG antibodies [32].

Anti-phospholipid antibodies are a group of immune proteins (antibodies) that the body mistakenly produces against itself in an autoimmune response to phospholipids [33]. The occurrence of antiphospholipid antibodies in relationship with SCA increases the risk of thrombotic events, as both SCA and APS antibodies are associated with a prothrombotic state [34]. This involves stimulating increase binding to prothrombin to phospholipid surfaces with consequent thrombin at the site of injury. Thrombotic problems are the main cause of morbidity in patients with antiphospholipid syndrome [35].

Other studies of SCA patients have reported an increased frequency of APLA antibodies in SCA patients, ACA IgG 65%, 35% IgM [36]. The increase frequency obtained from this study were ACA IgG 4%, IgM 2%; β2GP1IgG 5%, IgM 3% and this is similar with the findings from Olayimka who also worked in Nigeria sickle cell anaemia and found frequencies of IgG 8.0%, IgM 7.1% [29,37]. Other studies also reported that immunoglobulin IgG or IgM to phospholipid occur in SCA as a result of autoimmune disease, reaction to infections or drugs [38]. Such infectious diseases in SCA include viral, bacterial, parasitic and spirochaetal which can be transient and non-pathogenic [39]. This shows that individuals with sickle cell anaemia are more prone to having antiphospholipid antibodies than healthy individuals, and stresses the need for steady monitoring of these APLA in SCA. It has been established that antiphospholipid antibody can be to be associated with severe painful crisis, acute chest syndrome, osteomyelitis, avascular bone necrosis, arthritis, convulsions, spontaneous abortions and leg ulcerations in patients with sickle cell disease [40], principally caused by small blood vessel obstruction by sickle erythrocytes [29].

APLA is characterized by thrombosis and/or pregnancy morbidity with the persistent presence of lupus anticoagulant (LAC), anti-cardiolipin (aCL) and/or anti-β2glycoprotein I (aβ2GPI) antibodies. Chayoua *et al*., (2020) on their findings reported IgM/IgG of ACA and/or β2GPI was significantly correlated with thrombosis and pregnancy morbidity ranging from 3.5% to 5.4% and 5.7% to 12.3%, respectively [41]. Another study by Espinosa *et al.,* (2008) found that 10% to 15% of women with recurrent miscarriage are found to have positive APLA [42]. In this study it was observed that 18% of them are taking herbal medication and could be that many phytomedicines have been identified as potential antisickling agents Imaga et al., (2013) [43] *Carica papaya* leaf extract inhibited formation of sickle cells under severe hypoxia, with only 0–5% sickle cells at 40 mins compared with untreated SS cell suspensions which had over 60% sickle cells [43].

Conclusion

The elevated levels of APL antibody in patients with SCA may serve as a tool for the monitoring and surveillance of disease severity and thus a treatment and prognostic index for the improvement of the quality of care of these patients.

Limitations

The tests carried out to detect these antibodies were done once because the high cost of reagents made it difficult to do the assay longitudinally and this made it impossible to truly determine if they were transient or not because a positive finding after 12 weeks may suggest a tendency to having the antiphospholipid syndrome.

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Non-conflict of Interest

I ensure transparency and accountability during the course of my work. Also maintain objectivity and impartiality. I ensure high level of integrity and credibility. I comply with regulatory requirement.

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