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ORIGINAL RESEARCH

Plasma Lipid Levels in Relation to Disease Severity in Sickle Cell Anaemia in Abakaliki, Southeast Nigeria

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Abstract

Background: Dyslipidaemia has been implicated in the pathophysiology of sickle cell disease (SCD) complications; hence its role requires further elucidation.
Objectives: To investigate the relationship between disease severity and plasma lipid levels of patients with sickle cell anaemia.
Methods: A cross-sectional study design was used for the survey. A total of 50 patients with sickle cell anaemia and 50 controls without SCD were recruited for the study. The clinical data and plasma lipid levels of lipids and haemoglobin parameters were analysed.
Results: The majority of the participants were aged 18-25 years. Total plasma cholesterol and HDL-C were significantly lower in individuals with SCA compared with the controls (3.3±1.2 vs 4.2±1.2; p<0.001) and (1.3±0.5 vs 1.5±0.4; p = 0.038) respectively. Most patients with SCA had moderate disease severity (24; 48%). There was no statistically significant difference in the plasma levels of total cholesterol and HDL-C across the disease severity groups of SCA (p = 0.694 and 0.262). There was also no significant correlation between total cholesterol, HDL-C, and markers of haemolysis, haemoglobin F, and haemoglobin S levels.
Conclusion: SCA is characterised by lower mean plasma TC and HDL than controls. However, no relationship was found between TC, HDL levels and SCD disease severity, markers of haemolysis, HbF and HbS levels. Further studies are required to ascertain the implications of plasma lipid levels in SCD.

Keywords: Cholesterol, Haemoglobinopathy, High-Density Lipoprotein-Cholesterol, Sickle Cell Disease, Total Cholesterol.

Introduction

Sickle cell anaemia (SCA) is a form of haemoglobinopathy due to substituting glutamic acid with valine at position 6 of the β-globin chain, leading to the synthesis of haemoglobin S (HbS). [1] The disease is characterised by red cell rigidity, poor tissue perfusion with attendant hypoxia, haemolysis, chronic inflammation, and multiple organ damage. [2-3] It is a known cause of reduced life expectancy in developing countries due to the lack of resources for adequately

managing this disorder. [1] The underlying pathophysiology in sickle cell anaemia, which leads to diverse clinical presentations, is the polymerisation of HbS, which distorts the red cell membrane architecture. Other mechanisms include impaired biorheology and increased adhesion-mediated vaso-occlusion, haemolysis-mediated endothelial dysfunction, and sterile inflammation with elaboration of inflammatory molecules.

Cholesterol is critical for steroid synthesis, cellular membrane formation and bile acid synthesis. Cholesterol is a red cell membrane component, contributing to its flexibility. Chylomicrons (CM), very low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) are produced as a result of cholesterol being delivered to tissues in apolipoprotein-packaged form. [4-5]

Dyslipidaemia refers to lipid metabolism disorders, which could be an elevation or decrease in plasma concentration of lipoproteins. They are related to various pathogenic states with particular affectation of the cardiovascular system. Dyslipidaemia may be primary from a genetic cause or secondary to systemic disease, diet or drugs. Abnormal increase in LDL-C is a known risk factor in cardiovascular disease as it leads to premature atherosclerotic changes of vessels. At the same time, HDL-C is anti-atherogenic and anti-inflammatory and primarily functions to transport cholesterol from the peripheral tissues to the liver, playing a role in the biodistribution of lipids. [6] Cholesterol has been established to play a central role in atherosclerosis, which has mechanisms similar to those observed in vasculopathy of sickle cell anaemia, including prevention of the release of nitric oxide, dysfunctional endothelial function, platelet aggregation and activity.[7] Atherosclerosis is characterised by increased accumulation of cholesterol in arterial wall macrophages, but atheromas are not found in SCD; instead, the vasculopathy in SCD is due to lack of nitric oxide following intravascular haemolysis and release of arginase. [8] The features of SCD with haemolysis-vasculopathy-associated complications include pulmonary hypertension, stroke, and priapism, which are manifestations of SCA associated with vasculopathy. [9]

Disease severity in SCA helps to prognosticate and stratify patient management. Some plasma lipids have been identified in previous studies to impact significantly on the severity of SCD. [10-12] Dyslipidaemia has been associated with sickle cell anaemia as a possible causative factor in the haemolysis and inflammatory processes observed in the condition, with attendant morbidity and mortality. [3,13] The lipid profile in sickle cell anaemia is typified by low levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) but increased levels of triglycerides (TG)levels. [1, 3, 11, 14] Dyslipidaemia is a risk factor for coronary artery disease and pulmonary hypertension in sickle cell disease and requires more evaluation. [2]

Literature on the status of plasma lipids in patients with SCD needs to be improved in southeast Nigeria, while global data are conflicting. In some studies, the severity of anaemia in SCA has been associated with the level of HDL-C. The level of HDL-C correlates well with the level of haemoglobin F (HBF), which is essential in reducing untoward consequences of SCD. [5,8] Moreover, HDL-C levels are inversely proportional to lactate dehydrogenase (LDH) level, a biomarker of haemolysis in SCA. Higher levels of LDH are associated with the severity of haemolysis. [8] Different studies have also noted low levels of total cholesterol and elevated triglycerides to influence the severity of anaemia and associated effects in SCD. [8] However, another study

reported no significant correlation between lipid levels and disease severity in patients with SCA. [9]

Given these discrepancies, this study was carried out to determine the blood lipid profile in SCA patients in Abakaliki, southeast Nigeria. The study evaluated the relationship between the blood lipid profile and disease severity in SCA.

Methods

This was a cross-sectional study conducted over five months (August to December 2022).

Study participants

Fifty subjects with HbSS attending the Sickle Cell Centre at the Alex Ekwueme Federal University Teaching Hospital Abakaliki (AEFUTHA), Southeast Nigeria while the controls were fifty age- and sex-matched controls aged 18 years and above. The controls were randomly selected from voluntary blood donors attending the blood donor clinic were recruited for this study.

Ethical considerations

Ethical approval for the study was obtained from the Hospital Research and Ethics Committee (NHREC 16/05/22/127). Informed written consent was obtained from the subjects. Patients' hospital records and a structured, interviewer-administered questionnaire were used to collect the participants' demographic and relevant clinico-laboratory data.

Inclusion criteria

Adult patients with HbSS confirmed with High-Performance Liquid Chromatography. Additional inclusion criteria for the cases included no history of crises in the last month, no history of blood transfusion in the preceding three months and an overnight fasting of about 12 hours duration. The controls were characterised by HbAA phenotype by haemoglobin electrophoresis and aged 18 years and above.

Exclusion criteria

Patients with recent history of crises, history of hypertension, and diabetes mellitus were excluded from the study. Moreover, those who did not consent to the study, those who were currently on lipid-lowering medications and those whose haemoglobin phenotype was not HbSS were excluded.

Evaluation of disease severity

Disease severity was determined and graded using the protocol recommended by Okocha *et al.* for SCD patients. [15] The patients were allocated scores for the following parameters: total white blood cell count, haemoglobin levels, transfusion data, and number of lifetime complications. The total severity scores were then stratified as <3 for mild disease, 3-5 for moderate disease, while scores >5 defined severe disease.

Laboratory analysis

Eight millilitres of venous blood were drawn from each participant at enrolment following a 12-hour fast. Three and five millilitres were dispensed into commercially prepared sodium ethylenediaminetetraacetic acid (EDTA) and lithium heparin sample tubes to analyse haematological and biochemical parameters, respectively. Haematological parameters, including full blood counts, were carried out using BC 5300 Mindray Haematology Analyzer. Haemoglobin genotyping was performed by high-performance liquid chromatography on an HPLC/Variant II haemoglobin testing system (Bio-Rad, Hercules, California, USA) to confirm the diagnosis of SCA. Biochemical assays of total cholesterol, high-density lipoprotein, and lactate dehydrogenase were performed using Selectra pro-XS biochemistry analyser (Elitech Group, Netherlands). Haematological and biochemical tests were conducted at the Research Laboratory of AEFUTHA.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 23 software (IBM, Armonk, New York, USA). Continuous variables, including age, haematological parameters, Hb variants, total cholesterol, HDL, and LDH, were summarised as mean, standard deviation, range and 95% confidence interval. Categorical variables, including frequency of crises, blood transfusions, and organ complications, were summarised as frequency and percentages. The differences in the mean of continuous variables between the SCD and control population were tested using the Student's t-test. In contrast, analysis of variance (ANOVA) was used to compare mean values of continuous variables between SCD severity groups. The differences in the proportion of categorical variables were tested using the Chi-Square test. Pearson's correlation test was used to test the relationship between total cholesterol, HDL and LDH with haemoglobin, levels of Hb variants, and SCD severity score with age, Hb and HB variants. *P* value ≤ 0.05 was considered statistically significant.

Results

Fifty patients with SCA and 50 age and sex-matched HbAA controls participated in the study. The majority of the participants were students (Table I).

Table I: Sociodemographic characteristics of the study population

Characteristics	*SCA* *n (%)*	*Controls* *n (%)*	*Statistics*	*p-value*
Age group				
18 – 24	33 (66.0)	41 (82.0)		
25 – 29	9 (18.0)	6 (12.0)		
30 – 34	5 (10.0)	1 (2.0)	Fishers	0.174
35 – 39	0 (0.0)	1 (2.0)		
≥40	3 (6.0)	1 (2.0)		
Sex				
Male	25 (50.0)	23 (46.0)	$\chi^2 = 0.160$	0.689
Female	25 (50.0)	27 (54.0)		
Education				
Secondary	21 (42.0)	0 (0.0)		
Undergraduate	27 (54.0)	45 (90.0)	Fishers	<0.001
Postgraduate	2 (4.0)	5 (10.0)		
Marital status				
Single	44 (88.0)	48 (96.0)	Fishers	0.269
Married	6 (12.0)	2 (4.0)		
Occupation				
Students	34 (68.0)	45 (80.0)		
Business/trading	6 (12.0)	5 (10.0)	Fishers	0.194
Civil servants	3 (6.0)	3 (6.0)		
Artisan/ Unemployed	4 (8.0)	2 (4.0)		
Corp member	3 (6.0)	0 (0.0)		

In Table II, the mean red cell count, haemoglobin levels and haematocrit of the SCA patients were significantly lower than those of the control group (3.2±0.7×10^{12}/L vs. 4.8±0.7×10^{12}/L,

7.5±1.4g/dL vs. 12.3±1.2g/dL, 23.8±4.1% vs 37.2±3.7%; p<0.001 in each case). The SCA patients also had significantly higher mean LDH levels than the control group (759.5 ±379.6iu/L vs. 417.6±495.1iu/L; p <0.001). Total cholesterol and HDL were significantly lower in SCA patients compared to HbAA controls (3.3±1.2mmol/L vs. 4.2±1.2mmol/L; p<0.001) and (1.3±0.5 mmol/L vs. 1.5±0.4mmol/L; p = 0.038) respectively.

Table II: Mean age, blood count, haemoglobin distribution, LDH, and cholesterol distribution of the study population

Parameters	*SCA*	*Range*	*Controls*	*Range*	*p-value*
Age	23.8 ± 6.9	18 – 47	22.7 ± 4.6	17 – 43	0.332
Blood Parameters	Mean ± SD	95% CI	Mean ± SD	95% CI	
RBC (cells/mcL)	3.2 ± 0.7	3.0 – 3.4	4.8 ± 0.7	4.6 – 5.0	<0.001
Hb (g/dl)	7.5 ± 1.4	7.2 – 7.9	12.3 ± 1.2	12.0 – 112.6	<0.001
PCV (%)	23.8 ± 4.1	22.7 – 25.0	37.2 ± 3.7	36.1 – 38.3	<0.001
Haemoglobin variants					
A_2	3.5 ± 1.2	0.0 – 6.0			
F	5.5 ± 5.2	0.2 – 19.7			
S	82.5 ± 11.4	37.5 – 92.5			
A_{1c}	5.3 ± 4.1	0.0 – 13.2			
A_0	4.0 ± 4.7	0.0 – 38.1			
C	0.0	0.0 -			
LDH (IU/L)	759.5± 379.6	651.7 – 867.4	417.6 ± 495.1	276.9 – 558.3	<0.001
Lipid Parameters (mmol/L)					
Total cholesterol	3.3 ± 1.2	2.9 – 3.6	4.2 ± 1.2	3.9 – 4.6	<0.001
HDL	1.3 ± 0.5	1.2 – 1.4	1.5 ± 0.4	1.4 – 1.6	0.038

SCA – Sickle Cell Anaemia; RBC – Red Blood Count; Hb – Haemoglobin concentration; PCV – Packed Cell Volume; LDH – Lactate Dehydrogenase; HDL – High-Density Lipoprotein.

In Table III, the majority of the SCA patients, 24 (48%), had moderate disease severity. About 80% had 3 or fewer painful crises in the last year, while 17 (63%) have had only three or fewer blood transfusions during the previous 12 months. Avascular necrosis of the hip joints (3; 6%) and chronic pain syndrome (3; 6%) were the most common complications among the patients with SCA.

Table IV depicts that based on disease severity, there was no statistically significant difference in the levels of total cholesterol and HDL-C levels across the SCA disease severity groups (p = 0.694 and 0.262, respectively). Table V shows there was no significant correlation observed between total cholesterol and HDL-C and age (p = 0.776 and p = 0. 316 respectively), markers of haemolysis (Lactate dehydrogenase p = 0.502 and p = 0.024 and Haemoglobin concentration (p = 0.012 and p = 0.933) respectively. There was also no significant correlation between Total cholesterol, HDL, and haemoglobin F and S levels (p = 0.758; p = 0.930) and (p = 0.964; p = 0.890), respectively.

Discussion

The present study hypothesised a relationship between the levels of some plasma lipids and the severity of SCD. The mean total plasma cholesterol (TC) was lower in SCA patients than in the control group. From previous studies, hypocholesterolaemia is a documented

biochemical abnormality in patients with SCA. [16, 17] As seen in the general population, the relationship between low plasma cholesterol and increased mortality had been reported by Nago *et al.* and Koton *et al.*, whose studies concluded that cancer mortality, stroke mortality, and heart disease mortality were related to low plasma cholesterol. [18, 19].

Table III: Disease severity of the HBSS study population

Indices of disease severity	*N (%)*
Number of crises in the last one year	
0 – 1	22 (44.0)
2 – 3	18 (36.0)
>3	10 (20.0)
History of blood transfusion	27 (54.0)
Number of blood transfusions in the last one year	
≤3	17 (63.0)
>3	10 (37.0)
Organ complications	
AVN	3 (6.0)
Chronic pain syndrome	3 (6.0)
Ulcers	2 (4.0)
Pneumonia	2 (4.0)
Infertility	2 (4.0)
Retinopathy	2 (4.0)
Seizure disorder	1 (2.0)
Priapism	1 (2.0)
Massive splenomegaly	1 (2.0)
Disease severity	
Mild	14 (28.0)
Moderate	24 (48.0)
Severe	12 (24.0)

AVN – Avascular necrosis

Table IV: Distribution of body cholesterol and HDL based on the severity of SCD

	Mild n = 14 Mean ± SD (95% CI)	**Moderate n = 24 Mean ± SD (95% CI)**	**Severe n = 12 Mean ± SD (95% CI)**	**F value**	**P value**
Total cholesterol (mmol/L)	3.1±1.0 2.5 – 3.7	3.4±1.3 2.9 – 4.0	3.2±1.1 2.5 – 3.9	0.368	0.694
HDL-C (mmol/L)	1.2±0.3 1.0 – 1.4	1.4±0.6 1.2 – 1.7	1.1±0.3 1.0 – 1.3	1.377	0.262

HDL-C – High-Density Lipoprotein-Cholesterol

However, these studies could not interpret the exact relationship between low plasma cholesterol and these mortalities. Several hypotheses have been proposed to account for low cholesterol plasma levels among individuals with SCA. These include increased cholesterol

utilisation during the increased red blood cell synthesis in SCA, dilution by a decrease in erythrocyte bulk, and increased plasma volume and lower cholesterol production due to diminished liver function. [20] In understanding the hypotheses of increased utilisation of cholesterol synthesis during erythropoiesis in SCA, cholesterol is known to be mainly conserved through enterohepatic circulation, and the synthesis of new RBC membranes will likely consume recycled cholesterol from haemolysed erythrocytes. There are also reports of the unknown mechanism of the haemoglobin S gene inducing hypocholesterolaemia. At the same time, it has been noted that SCA rarely co-exists with conditions associated with secondary hyperlipidaemia, like diabetes mellitus. [21-22]

Table V: Correlations of TC, HDL-C with age, haematocrit, LDH and Hb variants

	TC		*HDL-C*	
	R	p-value	R	p-value
Age	0.041	0.776	-0.145	0.316
Hb	0.164	0.256	-0.012	0.933
PCV	0.146	0.312	-0.037	0.800
LDH	-0.097	0.502	0.024	0.867
Haemoglobin variants				
A_2	-0.210	0.143	0.058	0.689
F	0.045	0.758	-0.013	0.930
S	0.007	0.964	-0.020	0.890
A_{1c}	-0.221	0.123	0.075	0.604
A_0	0.046	0.754	-0.041	0.780
C	0.076	0.601	-0.069	0.632

TC – Total Cholesterol; HDL-C – High Density Lipoprotein-Cholesterol; Hb – Haemoglobin concentration; PCV – Packed Cell Volume; LDH – Lactate dehydrogenase

The patients with SCA in the present study had significantly lower HDL-C levels than the control group. This observation is in agreement with previous studies. [12, 23-25] A low HDL-C level is undesirable because HDL-C possesses anti-inflammatory and vasoprotective functions. HDL-C can inhibit low-density lipoprotein cholesterol (LDL-C) oxidation and other inflammatory complex formation. [26] Recent data have revealed the participation of HDL-C in the vascular environment regarding haemolysis and anaemia, thereby suggesting the potential involvement of HDL-C in modulating haemolysis and vascular dysfunction. [27] In SCA, cell-free haemoglobin (Hb), which is released into the blood after haemolysis, might alter the inflammatory properties of high-density lipoprotein cholesterol (HDL-C). HDL-C turns pro-inflammatory from being anti-inflammatory; hence, HDL-C becomes pro-inflammatory.

Conversely, some studies have reported higher HDL-C levels in SCA patients. [28, 29] This variation may be due to age, gender, body mass index, diet composition, smoking, sample size, disease severity, and other underlying diseases and treatment regimens. [30]

Most of the patients with SCA in the current study had moderate disease. This is in keeping with a previous report in Nigeria. [15] Similar to the opinion of Ebele *et al.* [16], the present study did not find any significant relationship between TC, HDL-C plasma levels, and disease severity in SCA patients. Moreover, no correlation was found between total cholesterol and HDL-C plasma levels and markers of haemolysis (LDH

and haemoglobin concentration), Hbs S, and HbF levels. Low plasma lipid levels were not isolated to SCA but have been reported in other kinds of anaemia, both haemolytic and non-haemolytic. This biochemical abnormality may be a result of the impact of anaemia on lipid metabolism generally rather than a mechanism peculiar to SCA pathology. However, Conceição da Guarda *et al.* and Emokpae *et al.* reported relationships between these markers, disease severity, and lipid levels. [31, 32] The finding of Emokpae may be attributable to age differences in the study population and the larger sample size of their study.

Although the current study could not establish a significant correlation between the levels of some lipids and disease severity in SCA, it demonstrated lower mean levels of HDL-C and TC among individuals with SCA compared to the control group. This agrees with other studies that reported decreased total cholesterol, HDL-C, and LDLC levels among SCA individuals. These observations may highlight the need for future research in this direction.

Limitations

The limitations of this study may include a small sample size, which may limit the power of the research and the inability to include the participants' dietary and exercise history in the study's scope.

Conclusion

This study found that plasma TC and HDL-C are lower in SCA compared to individuals with HbAA. However, the study did not show any relationship between these plasma lipids and disease severity, markers of haemolysis, Hb F and HbS levels.

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Authors' Contributions: NOC conceptualised the study while EO participated in the design of the study. NOC, EO and OHC did data analysis and interpretation. ACO, NFO and all the other authors contributed to drafting the manuscript and revising the draft for sound intellectual content. All the authors approved the final version of the manuscript.

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References

1. Gomina M, Ayedoun M, Salifou T, Aidewou D, Akpona S. Prevalence and Factors Associated with Dyslipidaemia in Adults with Sickle Cell Disease in Parakou (Benin). Adv Biochem 2020;8:11–15. https://doi.org/10.11648/j.ab.20200801.12.

2. Kaddam L, Fadl-Elmula I, Eisawi OA, Abdelrazig HA, Saeed AM. Acacia Senegal (Gum Arabic) Supplementation Modulate Lipid Profile and Ameliorated Dyslipidaemia among Sickle Cell Anaemia Patients. J Lipids 2019; Article ID 3129461. https://doi.org/10.1155/2019/3129461.

3. Aleluia MM, Concelcao da Guardia C, Santiago RP, Fonseca TCC, Neves FI, Quinto de Souza R, *et al.* Association of classical markers and establishment of the dyslipidaemic sub-phenotypes of sickle cell anaemia. Lipids Health Dis 2017;16:74. https://doi.org/10.1186/s12944-017-0454-1.

4. Goldstein JL, Brown MS. A century of cholesterol and coronaries: from plaques to genes to statins. Cell. 2015;161:161–172. https://doi.org/10.1016/j.cell.2015.01.036.

5. Zhang Z, Zanotti I, Reilly MP, Glick JM, Rothblat GH, Rader DJ. Overexpression of apolipoprotein A-I promotes the reverse transport of cholesterol from macrophages to feces in vivo. Circulation 2003;108:661–663. https://doi.org/10.1161/01.CIR.0000086981.09834.E0.

6. Navab M, Reddy ST, Van Lenten BJ, Buga GM, Hough G, Wagner AC, *et al.* High-density lipoprotein and 4F peptide reduce systemic inflammation by modulating intestinal oxidised lipid metabolism: novel hypotheses and review of the literature. Arterioscler Thromb Vasc Biol 2012;32:2553-2560. https://doi.org/10.1161/ATVBAHA.112.300282.

7. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature. 2011;473:317–325. https://doi.org/10.1038/nature10146.

8. Kato GJ, Gladwin MT, Steinberg MH. Deconstructing sickle cell disease: reappraisal of the role of haemolysis in the development of clinical subphenotypes. Blood Rev 2007;21:37–47. https://doi.org/10.1016/j.blre.2006.07.001.

9. Kato GJ, Wang Z, Machado RF, Blackwelder WC, Taylor JGt, Hazen SL. Endogenous nitric oxide synthase inhibitors in sickle cell disease: abnormal levels and correlations with pulmonary hypertension, desaturation, haemolysis, organ dysfunction and death. Br J Haematol 2009;145:506–513. https://doi.org/10.1111/j.1365-2141.2009.07658.x.

10. Aleluia MM, da Guarda CC, Santiago RP, Fonseca TC, Neves FI, de Souza RQ, *et al.* Association of classical markers and establishment of the dyslipidemic sub-phenotype of sickle cell anemia. Lipids Health Dis 2017;16:74. https://doi.org/10.1186/s12944-017-0454-1.

11. Zorca S, Freeman L, Hildesheim M, Allen D, Remaley AT, Taylor JG, *et al.* Lipid levels in sickle-cell disease associated with haemolytic severity, vascular dysfunction and pulmonary hypertension. Br J Haematol 2010;149:436-445. https://doi.org/10.1111/j.1365-2141.2010.08109.x.

12. Teixeira RS, Arriaga MB, Terse-Ramos R, Ferreira TA, Machado VR, Rissato-Lago MR, *et al.* Higher values of triglycerides: HDL-cholesterol ratio hallmark disease severity in children and adolescents with sickle cell anaemia. Braz J Med Biol Res 2019;52:e8833-e8841. https://doi.org/10.1590/1414-431X20198833.

13. Ephraim RKD, Adu P, Ake E, Agbodzakey H, Adoba P, Cudjoe O, *et al.* Normal Non-HDL Cholesterol, Low Total Cholesterol, and HDL Cholesterol Levels in Sickle Cell Disease Patients in Steady State: A Case-Control Study of Tema Metropolis. J lipids 2016;2016:7650530. https://doi.org/10.1155/2016/7650530.

14. Gupta M, Sharma P, Vishwakarma SK, Bhalke L, Chandra UK. Study of lipid profile parameters abnormalities in patients with sickle cell disease from a single centre study in central India. Int J Adv Med 2020;7:912-915. https://doi.org/10.18203/2349-3933.ijam20202103

15. Okocha E, Onwubuya E, Osuji C, Ahaneku G, Okonkwo U, Ibeh N, *et al.* Disease Severity Scores and Haemogram Parameters in Nigerian Sickle J Blood Disord Transfus 2015;6:1000324. https://doi.org/10.18203/2340-3933.ijam20202103.

16. Ebele U, Olusola O, Benjamin A, Ayobami I, Akinsegun A, Adedoyin D, *et al.* Lipid Profile and Disease Severity in Sickle Cell Disease patients in Lagos State, Nigeria. Sierra Leone

J Biomed Res 2018;10:24-31. http://dx.doi.org/10.4314/sljbr.v10i2.2.

17. Nnodim JK, Opara AU, Nwanjo HU and Ibeaja OA. Plasma Lipid Profile in Sickle Cell Disease Patients in Owerri Nigeria. Pak J Nutr 2012;11:65-64. https://doi.org/10.3923/pjn.2012.64.65

18. Nago N, Ishikawa S, Goto T, Kayaba K. Low cholesterol is associated with mortality from stroke, heart disease, and cancer: the Jichi Medical School Cohort Study. J Epidemiol 2011;21:67-74.

19. Koton S, Molshatzki N, Bornstein NM, Tanne D. Low cholesterol, statins and outcomes in patients with first-ever acute ischemic stroke. Cerebrovasc Dis 2012;34:213–220. https://doi.org/10.1159/000342302.

20. Dantas MT, Lopes A, Ladeia AMT. Association Between Lipid Profile and Clinical Manifestations in Sickle Cell Anemia: A Systematic Review. Int J Cardiovasc Sci 2022;35:770-779. https://doi.org/10-36660/ijcs.20220010.

21. Oforofuo IAO, Adedeji MO. Effect of sickle cell gene expression on plasma cholesterol in a Nigerian population. Clin Biochem 1994;27:505-508. https://doi.org/10.1016/0009-9120(94)00049-2.

22. Zailaie MZ, Marzouki ZM, Khoja SM. Plasma and red blood cells membrane lipid concentration of sickle cell disease patients. Saudi Med J 2003;24:376-379.

23. Benazeer SJ, Bardapurkar JS, Vinod RB, Bardapurkar SJ. Evaluation of lipid profile status in sickle cell disease patients of North Maharashtra. Biomedicine 2016;36:50-54.

24. Seixas MO, Rocha LC, Carvalho MB, Menezes JF, Lyra IM, Nascimento VM, *et al.* Levels of high-density lipoprotein cholesterol (HDL-C) among children with steady-state sickle cell disease," Lipids Health Dis 2010;9:91-99. https://doi.org/10.1186/1476-511X-9-91.

25. Yalcinkaya A, Unal S, Oztas Y. Altered HDL particle in sickle cell disease: decreased cholesterol content is associated with haemolysis, whereas decreased Apolipoprotein A1 is linked to inflammation. Lipids Health Dis 2019;18:225-231. https://doi.org/10.1186/s12944-019-1174-5.

26. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-2897. https://doi.org/10.1001/jama.285.19.2486.

27. Ji X, Feng Y, Tian H, Meng W, Wang W, Liu N, *et al.* The mechanism of pro-inflammatory HDL generation in sickle cell disease is linked to cell-free hemoglobin via haptoglobin. PLoS One 2016;11:e0164264- e0164283. https://doi.org/10.1371/journal.pone.0164264.

28. Rahimi Z, Merat A, Haghshenass M, Madani H, Rezaei M, Nagel RL. Plasma lipids in Iranians with sickle cell disease: hypocholesterolemia in sickle cell anemia and increase of HDL-cholesterol in sickle cell trait. Clin Chim Acta 2006;365:217–220. https://doi.org/10.1016/j.cca.2005.08.022.

29. Samarah F, Srour MA, Dumaidi K. Plasma Lipids and Lipoproteins in Sickle Cell Disease Patients in the Northern West Bank, Palestine. BioMed Res 2021; Article ID 6640956, 8 pages. https://doi.org/10.1155/2021/6640956

30. Choy E, Sattar N. Interpreting lipid levels in the context of high-grade inflammatory states with a focus on rheumatoid arthritis: a challenge to conventional cardiovascular risk

actions. Ann Rheum Dis 2009; 68:460–469. https:/doi.org/10.1136/ard.2008.101964.

31. Conceição da Guarda C, Cocou Modeste Alexandre Yahouédéhou S, Pereira Santiago R, Felix de Lima Fernandes C, Santana dos Santos Neres J, Mateus de Jesus Oliveira A. Investigation of Lipid Profile and Clinical Manifestations in SCA Children. Disease Markers 2020; Article ID 8842362, 10 pages. https://doi.org/10.1155/2020/8842362.

32. Emokpae AM, Kuliya-Gwarzo A. The influence of decreased levels of high-density lipoprotein cholesterol on haematological indices in sickle cell disease patients. Ann Med Health Sci Res 2004;4:157-161. https://doi/org/10.4103/2141-9248.129020.