A Study of Lipid Profile in Sickle Hemoglobinopathy Patients and Its Correlation with Pulmonary Hypertension and Hemolysis

Article · July 2017

CITATIONS
0

READS
60

2 authors, including:

Arti Muley
Sumandeep Vidyapeeth University
30 PUBLICATIONS **95** CITATIONS

SEE PROFILE

ISSN- O: 2458 - 868X, ISSN –P: 2458 - 8687

International Journal of Medical Science and Innovative Research (IJMSIR)

IJMSIR : A Medical Publication Hub

Available Online at: www.ijmsir.com

Volume – 2, Issue – 4, July - August - 2017, Page No. : 27 - 34

A Study of Lipid Profile in Sickle Hemoglobinopathy Patients and Its Correlation with Pulmonary Hypertension and Hemolysis

Dr Nikhil Patel

Resident, Deptt. of Medicine, SBKS MIRC, Sumandeep Vidyapeeth, Piparia, Vadodara, Gujarat, India.

E-Mail Id: nikshans@gmail.com

Dr Arti Muley

Professor, Deptt. of Medicine, SBKS MIRC, Sumandeep Vidyapeeth, Piparia, Vadodara, Gujarat, India.

E-Mail Id: muleyarti40@gmail.com

Correspondence Author: Dr Arti Muley, Professor, Deptt. of Medicine, SBKS MIRC, Sumandeep Vidyapeeth, Piparia, Vadodara, Gujarat, India.

Contact No.: +91- 9879609196

E-Mail Id: muleyarti40@gmail.com

Conflicts of interest: None to Declare

Abstract

Introduction: This study was planned to assess the lipid profile of patients of sickle hemoglobinopathy coming to our hospital and its possible relationship to vasculopathic complications such as PAH and hemolysis.

Methodology: All suspected and known adult cases of sickle cell hemoglobinopathy were enrolled for the study. The patients confirmed to have sickle cell hemoglobinopathy were included in the study. All those patients with a history of taking lipid lowering drugs or history of acute illness during the two weeks prior to the assessment or any immunocompromised state or pregnancy were excluded. All included participants were subject to CBC, renal and liver function tests, serum lactate dehydrogenase (LDH), lipid profile, Chest X ray, ECG, 2D Echo and USG abdomen. Mean lipid values (triglycerides, cholesterol, high density lipoprotein, and low density lipoprotein levels) were measured and compared with TRV to see for any correlation. Bivariate correlations were assessed using the Spearman rank correlation coefficient.

Results: The mean total cholesterol in the participants was 113.42 ± 26.095 (mg%), mean LDL was 60.276 ± 23.10 (mg%), mean HDL was 28.60 ± 6.596 (mg%). Mean CHOL/HDL ratio was 4.11 ± 1.05(mg%) and mean triglycerides level was 124.72 ± 80.537(mg%). Thus, cholesterol, LDL and HDL levels were reduced in the study participants. A significant moderately negative correlation was noted between bilirubin and cholesterol, LDL and HDL levels (p = .031, .004 and .001 respectively). There was no correlation of lipid levels with pulmonary hypertension.

Conclusion: Sickle hemoglobinopathy is associated with low total cholesterol, low LDL-C and low HDL-C levels. However, reports regarding triglyceride levels in sickle hemoglobinopathy are inconsistent. SCD is also significantly associated with PH. Low lipid levels are associated with low atherogenesis and more severe hemolysis in patients with SCD but have no correlation with PH.

Keywords: Sickle hemoglobinopahy, Total cholesterol, LDL, HDL, Pulmonary hypertension, hemolysis.

Introduction: Sickle-cell disease (SCD) is a genetic disorder transmitted via blood cells.[1] Homozygous HbS disease (HbSS) is the most common form of SCD found, and it is an autosomal recessive disorder first described by Herrick in 1910. There are many sickle-cell cases in Africa, occurrence is almost three quarters. A recent WHO report estimation is that around 2% of newborns in Nigeria has been affected by sickle cell hemoglobinopathy, around total of 150,000 affected children born every year in Nigeria alone.[2] In the USA people with sickle cell disease are about 1 in 5,000 mostly concerning Americans of Sub-Saharan African origin, as per the National Institutes of Health.[3]

In the United Kingdom, around 12,000 - 15,000 people suffer from sickle hemoglobinopathy (mostly SCD). England alone is estimated to have approx 250,000 carriers of the condition.s[4] In Saudi Arabia Approximately 4.2% of the residents are carriers of sickle-cell trait and 0.26% of them have sickle-cell disease. Eastern province has reported the highest occurrence that is around 17% carriers of the gene and 1.2% with sickle-cell disease.[5]

In India (mostly central part) and Nepal Sickle-cell disease is common in ethnic groups, who split a genetic linkage with African communities, the prevalence being 0-35%. In India certain states like Maharashtra, Gujarat, Chattisgarh, Jharkhand, Orissa and Madhya Pradesh are having a major public health problem due to it.

Problems in sickle cell disease typically begin at around 5 to 6 months of age. The most common abnormality of SCD is vaso-occlusion and premature RBC destruction. Chronic hemolysis is the cause of anemia, oxidant stress, reduced absorption of nitric oxide (NO) and endothelial activation in SCD[6-10] It is now known that progressive hemolysis-associated vasculopathy may be the starting point of some complications of SCD like cutaneous leg ulceration, priapism and stroke.[11] The normal life probability in the developed world is 40 to 60 years.PAH which is an extensive vascular disease of the lungs has now been recognised as an important complication likely to be present in about one-third of adult SCD population. It is also linked with early mortality.[12,13] In the more ill patients, increased TRV is associated with histopathologic changes similar to atherosclerosis such as plexogenic changes and hyperplasia of the pulmonary arterial intima and media.[14-17]

Atherosclerosis is aggravated by oxidant stress. Oxidant stress is seen in SCD also where total and low density lipoprotein cholesterol are reported to be low.[18-22] However, reports of low HDL cholesterol (HDL-C)[22,23] and increased triglyceride[18,24] (contributory factors of cardiovascular disease) in SCD patients have also been seen. We planned this study to assess the serum lipid profile of patients of sickle hemoglobinopathy (SH) coming to our hospital and its possible relationship to vasculopathic complications such as PAH as many commonly used drugs are available to regulate serum lipids.

Methodology: This study was done to identify association between dyslipidemia and clinical manifestations of sickle cell hemoglobinopathy like anemia, hemolysis and PAH. It was conducted for one and a half year in the Deptt of medicine of a tertiary care hospital in west Gujarat. It was started after procuring approval for the study from the institutional ethics committee.

All suspected and known cases of sickle cell hemoglobinopathy (> 18 years in age) coming to deptt. of medicine were enrolled for the study. The patients confirmed to have sickle cell hemoglobinopathy who gave written informed consent for participating in the study were included in the study. All those patients with a history of taking lipid lowering drugs or history of acute

illness during the two weeks prior to the assessment or any immunocompromised state or pregnancy were excluded. The patients who did not give consent were also excluded from the study. All cases enrolled were subjected to Hemoglobin (Hb) electrophoresis for confirmation of sickle cell hemoglobinopathy. However, the test was not done for those who had already been confirmed with electrophoresis. All included participants were subject to CBC, renal and liver function tests, serum lactate dehydrogenase (LDH), lipid profile, Chest X ray, ECG, 2D Echo and USG abdomen. Laboratory evaluations were performed in the institutional pathology and biochemistry labs. Lipid profile samples were collected in the morning (not necessarily the first sample in the morning) after fasting of about ten hours. All participants were also screened for pulmonary hypertension by echocardiography, measuring the tricuspid regurgitant velocity (TRV). TC < 200 mg%, HDL-C 60 – 160 mg%, LDL-C 30 – 60 mg%, HDL/LDL ratio upto 4 and TC/HDL ratio upto 6 were considered normal. Raised serum bilirubin with anemia in absence of liver disease was considered as a marker of hemolysis. As criteria for PAH, a TRV of 2.5–2.9 m/s (at least two standard deviations above the mean) was considered representative of borderline or mildly elevated PASP, whereas a TRV 3.0 m/s or higher (approximately three standard deviations above the mean) was considered significantly elevated PASP.

Characteristics of study participants are presented as mean or median and percentage of participants as applicable. Mean lipid values (triglycerides, cholesterol, high density lipoprotein, and low density lipoprotein levels) were measured and compared with TRV to see for any correlation. Bivariate correlations were assessed using the Spearman rank correlation coefficient. Logistic regression models were used to investigate the associations between both lipid variables and other characteristics, with TRV.

Results: Total 80 patients were enrolled and after excluding 30 for various reasons, total 50 patients were included in the study and were analysed. Mean age of the participants was 31 ± 12.08 years. 20 (40%) were females and 30(60%) were males. Majority patients were males and were from the younger age groups, with pulse and blood pressure in the normal range. Amongst the various presenting complaints in our study, most common presenting complaint was joint pain (54%) followed by fever (26%) and breathlessness (10%). On 2D Echo, 5(10%) patients had moderate PAH, 3(6%) patients had severe PAH, 1(2%) patient had mild PAH. 2 (4%) patients had mild MR and 1(2%) each had mild AR, moderate MR and RHD. All patients who had PAH were sickle homozygous. None of the sickle cell trait group had PAH. Average haemoglobin was reduced, average TLC and bilirubin were elevated with liver enzymes and mild elevation of blood urea and serum creatinine were also present. Mean Hb was 7.96 ± 2.60 gm/dl. Mean TLC was 13,700 ± 10,230 / cu.mm. Mean urea was 39.86 ± 41.948 (mg%) and mean creatinine was 1.38 ± 1.21 (unit). Mean serum bilirubin, SGOT and SGPT were 3.05 ± 3.16 (mg%), 315.66 ± 897.118 (IU/L) and 157.04 ± 386.362(IU/L) respectively.

Table 1: Lipid reports of the study participants

Parameter(unit)	**Mean ± Std. Deviation**
T.cholesterol (mg%)	113.42 ± 26.095
LDL (mg%)	60 ± 23.1005571
HDL (mg%)	28.60 ± 6.596
Chol:HDL (mg%)	4.1116 ± 1.0581450
Trig (mg%)	124.72 ± 80.537

The mean total cholesterol in the participants was 113.42 ± 26.095 (mg%), mean LDL was 60.276 ± 23.10 (mg%), mean HDL was 28.60 ± 6.596 (mg%). Mean CHOL/HDL ratio was 4.11 ± 1.05(mg%) and mean triglycerides level was 124.72 ± 80.537(mg%). Thus, cholesterol, LDL and HDL levels were reduced in the study participants.(Table 1).

On analysing correlation between age, HBF, LDL, HDL and total cholesterol in all sickle hemoglobinopathy patients, it was observed that there was a significant moderately positive correlation of HBF with LDL and total cholesterol. (Table 2) On analysing correlation between bilirubin and lipid levels in sickle hemoglobinopathy patients, a significant moderately negative correlation was noted between bilirubin and cholesterol, LDL and HDL levels. (Table 3)

Table 2: Correlation of Age, total cholesterol, HBF, LDL and HDL in sickle hemoglobinopathy. (n=50).

Parameter		T.CHOL.	HBF	LDL	HDL	TRIG
AGE	Pearson Correlation	.043	-.069	.067	.054	-.037
	P-value	.769	.635	.645	.711	.798
T.CHOL.	Pearson Correlation		.324	.783	.319*	.399
	P-value		.022	.000	.024	.004
HBF	Pearson Correlation			.327	-.083	.118
	P-value			.021	.568	.416
LDL	Pearson Correlation				.096	-.208
	P-value				.507	.147
HDL	Pearson Correlation					.001
	P-value					.996

Table 3: Correlation of bilirubin with total cholesterol, LDL, HDL, Chol: HDL, triglycerides.

		BILIRUBIN	T.CHOL.	LDL	HDL	CHOL:HDL	TRIG
BILIRUBIN	Pearson Correlation	1	-.306	-.402	-.339	.075	.240
	P-value		.031	.004	.016	.605	.093
T.CHOL.	Pearson Correlation		1	.783	.319	.512	.399
	P-value			.000	.024	.000	.004
LDL	Pearson Correlation			1	.096	.511	-.208
	P-value				.507	.000	.147
HDL	Pearson Correlation				1	-.628	.001
	P-value					.000	.996
CHOL:HDL	Pearson Correlation					1	.350
	P-value						.013

Analysis of correlation between PAH, LDL, HDL and total cholesterol showed that there was no significant correlation of PAH with LDL and HDL levels. (Table 4).

Table 4: Correlation of PAH with total cholesterol, LDL, HDL, Chol: HDL, triglycerides.

	T. chol.	LDL	HDL	Chol:HDL	Trig	PAH
T. chol.	1					
LDL	0.782578	1				
HDL	0.319103	0.095992	1			
Chol:HDL	0.51164	0.511061	-0.62752	1		
Trig	0.39912	-0.208	0.000784	0.349877	1	
PAH	0.100203	0.031952	0.043138	0.032192	0.105006	1

Discussion: Hypocholesterolemia and hypertriglyceridemia have been reported in sickle hemoglobinopathy cohorts worldwide since last four decades. Significant hypocholesterolemia with decreased LDL-C and HDL-C has been described in SCD patients in various studies.[25-27] It has also been reported to be a potential biomarker for clinical severity in SCD.[28] It has also been shown that with increasing severity of anemia, cholesterol (TC, HDL-C and LDL-C) levels decreased and triglyceride levels increased. Few studies have reported raised cholesterol content per RBC related with reduced plasma or serum cholesterol in SCD.[26, 29] In our study also, we found hypocholesterolemia and low LDL-C levels in patients of sickle cell hemoglobinopathy. Low levels of

LDL-C in SCD are consistent with the low levels of total cholesterol and can explain the virtual absence of atherosclerosis among SCD patients.

Decreased HDL-C and apoA-I are known risk factors for endothelial dysfunction. There are studies which have reported low HDL-C[30,31] and increased triglyceride levels[32,33] in SCD patients. They have been reported to be associated with PH in SCD.[34] In a study, lower HDL-C levels was reported to be associated with higher requirement of blood transfusions; which can be an indication of more severe disease.[35] In another study, higher HDL-C level in SCD patients was reported to be associated with lower risk of hemolysis and endothelial dysfunction. They also suggested that it may be due to the increased rate of blood marrow cell production during hemolytic crisis leading to high consumption of cholesterol. They also reported leukocytopenia, low monocyte count and thrombocytopenia, low levels of of hepatic and hemolytic markers and significantly lower VLDL-C, triglycerides and A1AT concentrations in SCD with higher HDL-C levels.[36,37] In our study also we observed a significant moderately negative correlation of bilirubin with cholesterol, LDL and HDL levels suggesting a more severe hemolysis in patients with lower levels of cholesterol, LDL and HDL.

Triglycerides have not been studied as widely as cholesterol in SCD, but a few studies have shown raised triglycerides.[32,33] Raised of plasma triglycerides levels have been shown to promote vascular dysfunction, leading to vasculopathy in coronary and cerebral arteries in the general population. However, in SCD and autoimmune diseases including systemic lupus erythematosus, scleroderma, rheumatoid arthritis, and mixed connective tissue diseases, they have been reported to predominantly affect the pulmonary vascular bed.[38] In a study, triglyceride concentration was also reported to be a stronger predictor of stroke than LDL-C or TC.[39] Raised triglyceride levels after a high-fat meal have been shown to induce oxidative stress and inflammation leading to endothelial dysfunction and vasoconstriction even in healthy controls.[40] However, in our study the participants didn't have hypertriglyceridimia. On the contrary we found that triglyceride levels were also reduced in our study population. Two other studies didn't show raised triglyceride levels in adult SCD subjects.[27]

Patients with the most severe forms of SCD (SS or Sβ0) phenotypes have been reported to have the most severe hemolytic anemia, with highest prevalence of vascular disease and pulmonary hypertension.[41,42] Although intravascular hemolysis causes oxidant stress leading to PH in SCD, atheromas are not typically present in SCD patients. This has been shown be due to low plasma total cholesterol and low density cholesterol levels in SCD patients. [25-27, 30-32] Thus, the vasculopathy of PH in SCD does not seem to be due to increased TC or LDL-C levels.

In last few years, echocardiographic screening studies done for detection of pulmonary hypertension in SCD have reported high prevalence of hemoglobinopathy associated pulmonary hypertension. Previously done studies also showed that TRV of 2.5 m/s or higher increased the risk of early mortality by about ten folds as compared to that in subjects of sickle cell disease with lower TRV. World health organisation has also shown association of pulmonary hypertension and severity in sickle patients. In our study also we observed high risk of pulmonary hypertension in SCD patients without any correlation to levels of lipids.

Thus, we observed hypocholesterolemia and low total, LDL-C and HDL-C levels, which were consistent with previous studies. However, only few studies have reported hypotriglyceridimia as in our study. As in other studies, we also observed significant presence of PAH in SCD

patients although it did not show any significant correlation with the lipid levels. We also observed moderately positive correlation of HBF with LDL and total cholesterol as well as a significant moderately negative correlation of bilirubin with cholesterol, LDL and HDL levels.

Conclusion: Sickle hemoglobinopathy is associated with low total cholesterol, low LDL-C and low HDL-C levels. However, reports regarding triglyceride levels in sickle hemoglobinopathy are inconsistent. SCD is also significantly associated with PH. Low lipid levels are associated with low atherogenesis and more severe hemolysis in patients with SCD but have no correlation with PH.

References

[1]." What Is Sickle Cell Disease?". National Heart, Lung, and Blood Institute. June 12, 2015.

[2]. WHO. "Sickle-cell anaemia - Report by the Secretariat" (PDF).

[3]. National Heart, Lung and Blood Institute. "Sickle cell anemia, key points".

[4]. "Inheriting sickle cell anaemia - Live Well - NHS Choices". www.nhs.uk.

[5]. Jastaniah W (2011). "Epidemiology of sickle cell disease in Saudi Arabia". Annals of Saudi Medicine. 31 (3): 289–93. doi:10.4103/0256-4947.81540. PMC 3119971.PMID 21623060.

[6]. Aslan M, Ryan TM, Adler B, Townes TM, Parks DA, Thompson JA, Tousson A, Gladwin MT, Patel RP, Tarpey MM, Batinic-Haberle I, White CR, Freeman BA. Oxygen radical inhibition of nitric oxide-dependent vascular function in sickle cell disease. Proc Natl Acad Sci U S A. 2001; 98:15215–15220.

[7]. Kato GJ, McGowan V, Machado RF, Little JA, Taylor Jt, Morris CR, Nichols JS, Wang X, Poljakovic M, Morris SM Jr, Gladwin MT. Lactate dehydrogenase as a biomarker of hemolysis-associated nitric oxide resistance, priapism, leg ulceration, pulmonary hypertension, and death in patients with sickle cell disease. Blood. 2006; 107:2279–2285.

[8]. Kaul DK, Liu XD, Fabry ME, Nagel RL. Impaired nitric oxide-mediated vasodilation in transgenic sickle mouse. Am J Physiol Heart Circ Physiol. 2000; 278:H1799–1806.

[9]. Nath KA, Shah V, Haggard JJ, Croatt AJ, Smith LA, Hebbel RP, Katusic ZS. Mechanisms of vascular instability in a transgenic mouse model of sickle cell disease. Am J Physiol Regul Integr Comp Physiol. 2000; 279:R1949–1955.

[10]. Reiter CD, Wang X, Tanus-Santos JE, Hogg N, Cannon RO 3rd, Schechter AN, Gladwin MT. Cellfree hemoglobin limits nitric oxide bioavailability in sickle-cell disease. Nat Med. 2002; 8:1383– 1389.

[11]. Kato GJ, Gladwin MT, Steinberg MH. Deconstructing sickle cell disease: reappraisal of the role of hemolysis in the development of clinical subphenotypes. Blood Rev. 2007; 21:37–47.

[12]. Ataga KI, Moore CG, Jones S, Olajide O, Strayhorn D, Hinderliter A, Orringer EP. Pulmonary hypertension in patients with sickle cell disease: a longitudinal study. Br J Haematol. 2006; 134:109–115.

[13]. Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, Brown B, Coles WA, Nichols JS, Ernst I, Hunter LA, Blackwelder WC, Schechter AN, Rodgers GP, Castro O, Ognibene FP. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med. 2004; 350:886–895.

[14]. Adedeji MO, Cespedes J, Allen K, Subramony C, Hughson MD. Pulmonary thrombotic arteriopathy in patients with sickle cell disease. Arch Pathol Lab Med. 2001; 125:1436–1441.

[15]. Graham JK, Mosunjac M, Hanzlick RL, Mosunjac M. Sickle cell lung disease and sudden death: a retrospective/prospective study of 21 autopsy cases and literature review. Am J Forensic Med Pathol. 2007; 28:168–172.

[16]. Haque AK, Gokhale S, Rampy BA, Adegboyega P, Duarte A, Saldana MJ. Pulmonary hypertension in sickle cell hemoglobinopathy: a clinicopathologic study of 20 cases. Hum Pathol. 2002; 33:1037– 1043.

[17]. Manci EA, Culberson DE, Yang YM, Gardner TM, Powell R, Haynes J Jr, Shah AK, Mankad VN.Causes of death in sickle cell disease: an autopsy study. Br J Haematol. 2003; 123:359–365.

[18]. Buchowski MS, Swift LL, Akohoue SA, Shankar SM, Flakoll PJ, Abumrad N. Defects in postabsorptive plasma homeostasis of fatty acids in sickle cell disease. JPEN J Parenter Enteral Nutr. 2007; 31:263–268.

[19]. El-Hazmi MA, Warsy AS, al-Swailem A, al-Swailem A, Bahakim H. Red cell genetic disorders and plasma lipids. J Trop Pediatr. 1995; 41:202–205 .

[20]. Marzouki ZM, Khoja SM. Plasma and red blood cells membrane lipid concentration of sickle cell disease patients. Saudi Med J. 2003; 24:376–379.

[21]. Shores J, Peterson J, VanderJagt D, Glew RH. Reduced cholesterol levels in African-American adults with sickle cell disease. J Natl Med Assoc. 2003; 95:813–817.

[22]. Stone WL, Payne PH, Adebonojo FO. Plasma-vitamin E and low plasma lipoprotein levels in sickle cell anemia patients. J Assoc Acad Minor Phys. 1990; 1:12–16.

[23]. Sasaki J, Waterman MR, Buchanan GR, Cottam GL. Plasma and erythrocyte lipids in sickle cell anaemia. Clin Lab Haematol. 1983; 5:35–44.

[24]. Morris CR, Kato GJ, Poljakovic M, Wang X, Blackwelder WC, Sachdev V, Hazen SL, Vichinsky EP, Morris SM Jr, Gladwin MT. Dysregulated arginine metabolism, hemolysis-associated pulmonary hypertension, and mortality in sickle cell disease. Jama. 2005; 294:81–90.

[25]. El-Hazmi MA, Jabbar FA, Warsy AS. Cholesterol and triglyceride level in patients with sickle cell anaemia. Scand J Clin Lab Invest. 1987; 47:351–354. [PubMed: 3602913].

[26]. Marzouki ZM, Khoja SM. Plasma and red blood cells membrane lipid concentration of sickle cell disease patients. Saudi Med J. 2003; 24:376–379. [PubMed: 12754538].

[27]. Shores J, Peterson J, VanderJagt D, Glew RH. Reduced cholesterol levels in African-American adults with sickle cell disease. J Natl Med Assoc. 2003; 95:813–817. [PubMed: 14527048].

[28]. Yuditskaya S, Tumblin A, Hoehn GT, Wang G, Drake SK, Xu X, Ying S, Chi AH, Remaley AT, Shen RF, Munson PJ, Suffredini AF, Kato GJ. Proteomic identification of altered apolipoproteinpatterns in pulmonary hypertension and vasculopathy of sickle cell disease. Blood. 2009;113:1122–1128. [PubMed: 19023114].

[29]. Akinyanju PA, Akinyanju CO. Plasma and red cell lipids in sickle cell disease. Ann Clin Lab Sci.1976; 6:521–524. [PubMed: 999221].

[30]. Sasaki J, Waterman MR, Buchanan GR, Cottam GL. Plasma and erythrocyte lipids in sickle cell anaemia. Clin Lab Haematol. 1983; 5:35–44. [PubMed: 6851435].

[31]. Stone WL, Payne PH, Adebonojo FO. Plasma-vitamin E and low plasma lipoprotein levels in sickle cell anemia patients. J Assoc Acad Minor Phys. 1990; 1:12–16. [PubMed: 2135691].

[32]. Buchowski MS, Swift LL, Akohoue SA, Shankar SM, Flakoll PJ, Abumrad N. Defects in postabsorptive plasma homeostasis of fatty acids in sickle cell disease.

JPEN J Parenter Enteral Nutr. 2007; 31:263–268. [PubMed: 17595432].

[33]. Kato GJ, Martyr S, Blackwelder WC, Nichols JS, Coles WA, Hunter LA, Brennan ML, Hazen SL,Gladwin MT. Levels of soluble endothelium-derived adhesion molecules in patients with sickle cell disease are associated with pulmonary hypertension, organ dysfunction, and mortality. Br J Haematol. 2005; 130:943–953. [PubMed: 16156864]

[34]. Yuditskaya S, Tumblin A, Hoehn GT, Wang G, Drake SK, Xu X, Ying S, Chi AH, Remaley AT, Shen RF, Munson PJ, Suffredini AF, Kato GJ. Proteomic identification of altered apolipoproteinpatterns in pulmonary hypertension and vasculopathy of sickle cell disease. Blood. 2009;113:1122–1128. [PubMed: 19023114].

[35]. Ohene-Frempong K, Steinberg MH. Clinical aspects of sickle cell anaemia in adults and children. In: Steinberg MH, Forget BG, Higgs DR, Nagel RL, editors. Disorders of Hemoglobin: Genetics, in Pathophysiology and Clinical Management. New York: Cambridge University Press; 2001. pp. 611–70.

[36]. Zorca S, Freeman L, Hildesheim M, Allen D, Remaley AT, Taylor JG, 6th, et al. Lipid levels in sickle-cell disease associated with haemolytic severity, vascular dysfunction and pulmonary hypertension. Br J Haematol. 2010;149:436–45.

[37]. AM Emokpae, A Kuliya-Gwarzo. The Influence of Decreased Levels of High Density Lipoprotein Cholesterol on Hematological Indices in Sickle Cell Disease Patients. Ann Med Health Sci Res. 2014 Mar-Apr; 4(2): 157–161.

[38]. 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.

[39]. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated metaanalysis of statins for stroke prevention. Lancet Neurol. 2009; 8:453–463.

[40]. O'Keefe JH, Gheewala NM, O'Keefe JO. Dietary strategies for improving post-prandial glucose, lipids, inflammation, and cardiovascular health. J Am Coll Cardiol. 2008; 51:249–255.

[41]. De Castro LM, Jonassaint JC, Graham FL, et al. Pulmonary hypertension in SS, SC and Sβ thalassemia: prevalence, associated clinical syndromes, and mortality. Blood. 2004;104:462a.

[42]. Villagra J, Shiva S, Hunter LA, Machado RF, Gladwin MT, Kato GJ. Platelet activation in patients with sickle disease, hemolysis-associated pulmonary hypertension, and nitric oxide scavenging by cell-free hemoglobin. Blood.2007;110:2166–72.