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Original article

Lipid modulatory effects of omega-3 fatty acids in children with sickle cell disease

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ABSTRACT

Background: Sickle cell disease (SCD) is one of the commonest prevalent blood inherited disorders, accompanied by inflammation, oxidative stress, pain and alterations in the membrane lipid composition. These have harmful impacts on the cardiovascular system, making it important to address the hypolipidemia observed in these patients at an early age, for effective treatment strategies. Omega-3 fatty acids are known to positively modulate the integrity of the erythrocyte membrane. Being a dietary supplement, having multi benefits, they seem to be ideal nutrients which could be tried out for lipid modulation in these patients. Objective- In this study, we explore the potential of omega-3 fatty acids in rectifying the lipid profile changes in pediatric SCD patients, in a small prospective interventional trial. Methods- Omega-3 fatty acids were orally given to forty-three pediatric patients with SCD for a period of six months, and their lipid profile markers studied, before and after the supplementation period. Results and Conclusion- Improvement in the lipid profile was observed after omega-3 supplementation, resulting in overall favorable changes. Omega3 fatty acids may therefore possibly be used as effective and safe add on supplements during therapy, to reduce the complications accompanying SCD.

1. Introduction

Sickle cell disease (SCD) is a monogenetic hereditary disorder resulting from a mutation in the β-globin gene leading to the production of abnormal haemoglobin S (HbS). Polymerization of HbS results in de oxygenation and sickling of RBCs, entrapping the fragile deformed sickle red blood cells in small blood vessels. This causes vaso-occlusive (VOC) pain and a cascade of hemolytic events, characterized by inflammation, intensified oxidative stress, tissue infarction complications, organ damage and compromised patient survival rate (Zorca et al., 2010).

Chronic hemolysis, reduces the bioavailability of nitric oxide (NO), thereby increasing oxidative stress and endothelial activation (Reiter et al., 2002). Progressive hemolysis in SCD, may be causative for the numerous complications like foot ulceration, stroke, pulmonary hypertension (PH), and priapism associated with the disease (Kato et al., 2007).

It has been observed that patients affected severely with SCD have severe hemolytic anemia, and also display highest occurrence of vascular disease and pulmonary hypertension (Taylor et al., 2008). One of the reasons responsible for this is the altered serum lipid levels in these patients'.

Abbreviations: SCD, sickle cell disease; VOC, Vaso-occlusive crisis; TG, triglycerides; TC, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein.

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Earlier studies report decreased serum total cholesterol (TC), low density lipoprotein (LDL), and high density lipoprotein (HDL) and increased serum levels of triglyceride (TG) in SCD patients, as compared to ethnically-matched healthy controls. Also, the decreases in cholesterol levels were associated significantly with severe anemia, whereas increased TG levels were associated with increased hemolysis, dysfunction in vascular system, and pulmonary hypertension. Alterations in the TG/HDL ratio were associated with endothelial dysfunction. Role of lipids in vasculopathy of SCD is gaining importance as these patients exhibit unique lipid profiles with decreased levels of both forms of apolipoprotein viz; apolipoprotein A (apoA), and apolipoprotein B (apoB), and also all types of cholesterol as compared to their normal healthy counterparts (Zorca et al., 2010).

Lipid markers are of dire importance in the vasculopathy of SCD. Though the levels of LDL-C is low in SCD, but the size, density and percentage also contributes to altered lipid profile as it is liable to permeate into the sub endothelial space where it then gets easily oxidized. Therefore irrespective of the levels of LDL-C, its proportion is a crucial factor in SCD, (Ekaterina et al., 2017; Samarah et al., 2021). Omega-3 fatty acids have been found beneficial in alleviating the symptoms related to atherosclerosis and other vascular diseases. It has been suggested that the consumption of marine omega-3 fatty acids is very beneficial in treating dyslipidemia, to subsequently reduce cardiovascular risk (Leslie et al., 2015).

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) forms of omega-3 fatty acids are not only the most widely present in supplements but also well researched for their cardiovascular benefits. They are known to improve arterial and endothelial function by positively modulating the membrane phospholipids. Moreover, their ability to combat platelet aggregation and inflammation by reducing the cytokine storm, make them ideal supplements for prevention of cardiovascular events (Kotue et al., 2019). Amongst the most sought after components in the functional food sector, omega-3 fatty acids stand out prominently, with immense health benefits. It has been observed that DHA was found to increase concentrations of HDL (Sagara et al., 2011), and a decrease in TG levels by 25–30% was observed on omega-3 supplementation (Zibaeenezhad et al., 2017). When omega-3 fatty acids were supplemented to individuals with either higher or lower TC as well as higher or lower TG than the normal cut off value, their blood levels of both TC and TG either increased or decreased towards the normal range. This therapeutic characteristic of omega-3 fatty acids to modulate serum lipids (Khan et al., 2017) prompted us to investigate the serum lipid profile in pediatric SCD patients.

We aimed to investigate the blood lipid picture in pediatric patients with sickle cell disease, and check the potential of omega-3 fatty acids in addressing the abnormalities.

2. Materials and methods

2.1. Subjects

We enrolled forty-three children with SCD (HbSS) aged 5–16 years in our study who were not on HU treatment. Of these 23 were male and 20 female. Twenty-six children were in the age group 5-10yrs and 17 of them were in the age group 11–16 years. The research protocol was approved by the local institutional Ethics Committee (reg no. 2/36/8390). Written consents were obtained from all guardians, parents, or caretakers of the patient.

We conducted a pilot interventional study on SCD pediatric patients at our research center. Patients were enrolled based upon their availability, procurement of their clinical information from the hospital, and consent by the parent. Since the study was conducted on children, we had to rely upon consent from patient's guardians for their enrollment. We could not include a control group in the study due to non-compliance. Therefore, we considered the pre supplementation values of the patients as their controls.

2.2. Inclusion criteria

Male and female SCD children who were in a steady state, and between 5 and 16 years of age, were included in the study. A steady haemoglobin and hematocrit level for more than 3–4 weeks was defined as the steady state. Patients from diverse ethnicities were enrolled without any bias of their physical attributes.

There was no diet restriction during the course of the study. Patients were allowed to consume their normal food. One of the common symptoms is belching, nausea and/or reflux after consuming fish oil products. The supplement was therefore asked to be taken just before meals so as to avoid this discomfort.

2.3. Exclusion criteria

Patients not in the 5–16 years range of age, had blood transfusion 10 weeks prior to enrollment; suffering from chronic diseases; or diagnosed with other complications or undertaking HU or omega-3 fatty acids treatment in the past 10 weeks of enrollment, were excluded.

2.4. Supplementation

Mango flavored omega-3 syrup procured from BRAINWISE Company, SPB Laboratories, HP, India, was supplemented, depending upon the patient's weights. Patients weighing between 11 and 24 Kg were asked to take 2 teaspoons of the syrup and those weighing 25 kg and above were asked to take 3 teaspoons of the syrup each day. Omega 3 fatty acid content in one teaspoon was 190 mg of DHA, and EPA 250 mg.

The use of HU could affect the frequency as well as severity of SCD complications. Hence we took patients who were not on hydroxyurea for our study.

2.5. Blood haemoglobin concentration was analyzed at the hospital before and after supplementation

A Sysmex KX-21 automated cell counter (Sysmex Corporation, Kobe Hyogo, Japan) was used for the measurement of hemoglobin concentration.

2.6. Lipid profile

Analysis of serum total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides was done using an automated Selectra ProM Chemistry Analyzer. Blood collection was done in a fasting state for all the patients. Three ml of blood was collected in non-EDTA tubes, and kept for half an hour at room temperature before centrifuging it for 15 min at 3000 rpm to obtain the serum fraction in the form of supernatant.

2.7. Statistical analysis

Results are presented as means with standard deviations using the statistical software SPSS 21. The paired student's *t*-test was used and p values of < 0.05 were considered as significant.

3. Results

All patients experienced similar vaso occlusive (VOC) crisis and other clinical complications at the beginning of the study. Excepting for dyspepsia observed in three children, at the beginning of the omega-3 syrup supplementation, there was no other adverse reaction observed by patients enrolled. This dyspepsia too decreased in 2–3 days. Furthermore, there was no occurrence of bleeding observed in any patient throughout the period of supplementation.

During the entire supplementation period, patients reported fewer minor complications like body ache, headache, mild fever and cold etc. that was manageable at home. None of the patients had to be hospitalized.

3.1. Hemoglobin concentration

Most patients were highly anemic with a Hb value < 8. A few were moderately anemic with Hb values between 8.0 and 10.9 g/dL. On omega3 supplementation, there was a significant increase (p- 0.045) in hemoglobin concentration from 7.26 ± 0.74 to 8.04 ± 1.59 as shown in Table 1.

3.2. Lipid profile

Total cholesterol, Triglycerides, HDL and LDL values were lower than normal in almost all the sickle cell disease children in our cohort. On supplementation with omega-3 fatty acids, these values improved significantly (Table 1).

Total cholesterol values ranged between 90.02 ± 18.65 which is much below the normal rage within 200 mg/dL. Omega 3 supplementation increased this value significantly to 112.69 ± 34.94. This increase was found to be irrespective of the gender. When further looked for changes with different ages, only males between the ages 5–10 years showed significant increase with a p value of 0.002. Males between 11 and 16 years exhibited an increase, but it was not significant (p value 0.309) (Table 2).

Triglyceride levels were lowered in all the patients with values ranging between 69.98 ± 19.10. This value increased significantly to 89.70 ± 15.59 in all the patients, irrespective of gender as well as age (Table 2).

HDL levels were found low in all the patients (21.70 ± 12.53) which increased significantly in all the patients after omega-3 supplementation to 34.81 ± 15.39 (Table 2). Here too age and gender did not show any difference in terms of significance.

LDL levels of the patients also were low in all the patients (64.93 ± 16.20) which increased significantly to 88.43 ± 23.85 after supplementation. This increase was found to be irrespective of the gender (Table 2). When further looked for changes with different ages, only older males aged between 11 and 16 years showed a significant increase. The males between 5 and 10 years exhibited an increase though not significant with p value 0.063.

TG/HDL ratio is considered high risk for clinical problems. In our study, the TG/HDL ratio was found to be 4.42 ± 3.52. This value significantly decreased to 3.28 ± 1.99 (p value 0.01) with supplementation (Table 3).The decrease was found significant in males, though the two age groups did not show significance. In females only the age group 11-16yrs showed a significant reduction (p value 0.043).

4. Discussion

Several clinical and pathological conditions such as splenectomy, hyperthyroidism, bone marrow failure, and certain types of hereditary and acquired anemias have been associated with low serum lipids. This decrease is implicative of intracranial hemorrhage, alterations in cell membrane structural changes, adrenal failure, sepsis, and an overall increased disease mortality. It has been observed that hypocholesterolemia is implicated in chronic anemias exhibiting increased erythropoiesis, because of the higher demand of cholesterol by the proliferating erythroid cells (Shalev et al., 2007).

The mainstay of preventive cardiology has been the modification of the lipid profile. The pursuit for lipid biomarkers in patients with SCD complications is ongoing due to the alterations exhibited. Under nutrition or malnutrition, has been reported to modulate the lipid profiles in SCD. As dietary fats form the exogenous source of body lipids, undernutrition and malabsorption of fats could also possibly lead to hypolipidemia (Elmehdawi 2008).

In our study, Hb levels in all the patients were significantly lower, in agreement with previous reports indicating SCD patients to be generally anemic. Here we examined triglyceride, and cholesterol levels in the serum of a small cohort of pediatric SCD patients from our university Hospital. Cholesterol (TC, LDL and HDL) levels as well as triglyceride levels were found decreased in all the patients along with lowered haemoglobin. Oral supplementation of fish oil omega-3 products usually results in stomach upsets, belching, nausea and bleeding in a few. In our study no bleeding was observed. This was probably because the blood of SCD patients is prone to aggregation. Nevertheless, a few patients did complain of minor gastric upsets at the beginning of the study, which subsided in 2 to 3 days.

Though hypocholesterolemia has earlier been observed in SCD patients in many studies globally, yet the treatment mode, its exact mechanism, association of altered lipids with the clinical manifestations observed and the eventual mortality is not totally understood. It was reported that cholesterol levels exhibit a U-shaped pattern in relation with rate of mortality amongst Korean adult males, which is increased when cholesterol concentrations is below 135 mg/dL as compared to when it is between 135 and 200 mg/dl.. Cholesterol is essential for many functions of the body and its minimum cut off value to maintain this requirement in adult males was found to be 135 mg/dL. Those with very low total cholesterol values of 135 mg/dL and lower exhibited higher rates of mortality as compared to those in the range 135 mg/dL up to the normal 200 mg/dL cut off value. Because of this U shaped pattern of cholesterol, the conventional value of <200 mg/dL should be considered with caution. (Yun-Mi Song et al., 2000).

Table 1
Hb and lipid profile levels of the patients before and after omega-3 supplementation.

Parameter	N	Pre (mean ± SD)	Post(mean ± SD)	'p' value
Hemoglobin concentration	43	7.26 ± 0.74	8.04 ± 1.59	0.04
Total Cholesterol	43	90.02 ± 18.65	112.69 ± 34.94	0.000
Triglyceride	43	69.98 ± 19.10	89.70 ± 15.59	0.000
LDL	43	64.93 ± 16.20	88.43 ± 23.85	0.000
HDL	43	21.70 ± 12.53	34.81 ± 15.39	0.000
TG/HDL ratio	43	4.42 ± 3.52	3.28 ± 1.99	0.01

Table 2
Lipid profile of male and female patients before and after omega-3 supplementation.

Parameter	N	Cholesterol	Triglyceride	HDL	LDL
Male	23	91.43 ± 19.54	69.97 ± 17.33	21.34 ± 13.18	60.05 ± 16.60
PRE (mean ± SD)		111.62 ± 6.53	89.96 ± 13.77	32.56 ± 15.37	85.86 ± 26.13
POST(mean ± SD		0.001	0.000	0.000	0.000
'p' value					
Male 5-10yrs	14	102.31 ± 6.87	63.57 ± 15.69	23.44 ± 14.53	64.05 ± 13.4876.64 ± 22.06.0.063
PRE (mean ± SD)		130.08 ± 32.26	86.37 ± 11.58	36.39 ± 15.45	
POST(mean ± SD		0.002	0.000	0.000	
'p' value					
Male 11-16yrs	9	78.83 ± 16.39	79.93 ± 15.56	18.06 ± 10.71	55.87 ± 19.73
PRE (mean ± SD)		83.31 ± 22.53	95.55 ± 15.67	26.60 ± 14.02	96.55 ± 27.10
POST(mean ± SD		0.309	0.008	0.009	0.000
'p' value					
Female	20	88.41 ± 17.94	69.99 ± 21.42	22.11 ± 12.08	70.55 ± 14.09
PRE (mean ± SD)		113.93 ± 3.92	89.41 ± 17.82	37.40 ± 5.38	91.38 ± 21.20
POST(mean ± SD		0.000	0.000	0.000	0.002
'p' value					
Female 5-10yrs	11	94.05 ± 18.49	71.50 ± 21.13	21.11 ± 1.88	68.4 ± 10.16
PRE (mean ± SD)		114.62 ± 38.85	92.03 ± 18.10	34.32 ± 16.24	85.68 ± 19.47
POST(mean ± SD		0.013	0.000	0.002	0.022
'p' value					
Female 11-16yrs PRE (mean ± SD)	9	84.71 ± 14.80	68.13 ± 22.90	23.33 ± 12.92	72.24 ± 18.13
POST(mean ± SD		117.60 ± 7.18	86.20 ± 17.99	41.16 ± 4.26	100.15 ± 20.7
'p' value		0.000	**0.004**	0.000	0.017

Table 3
Triglyceride/High density lipoprotein ratio of the patients before and after omega-3 supplementation.

ParameterTG/HDL	N	Pre (mean ± SD)	Post (mean ± SD)	'p' value
Males	23	5.53 ± 4.10	3.18 ± 2.01	0.017
Male 5-10yrs	14	4.09 ± 3.45	2.85 ± 1.45	0.076
Male 11-16yrs	9	6.61 ± 4.48	4.67 ± 2.58	0.058
Females	20	4.6 ± 3.37	3.59 ± 3.08	0.282
Female 5-10yrs	11	4.84 ± 3.55	4.59 ± 3.84	0.857
Female 11-16yrs	9	4.32 ± 3.31	2.36 ± 0.99	0.043

All the patients exhibited TC levels below 135 mg/dL which falls in the high risk for mortality range. Omega-3 supplementation was found to increase this value significantly. The normalizing effect of omega-3 fatty acids on cholesterol as well as triglycerides (Khan et al., 2017), is observed in this study, with increases in TG, TC, LDL as well as HDL values.

One of the postulated causes of hypocholesterolemia in SCD is attributed to lowered cholesterol synthesis, haemodilution, and a decreased transfer of cholesterol from the membrane to the circulating (HDL) due to decreases in lecithin-cholesterol acyltransferase activity (LCAT) (Daak et al., 2011). Lecithin, the major phospholipid of HDL and plasma cholesterol, are esterified by LCAT. Also, the downregulation of cholesterol biosynthesis takes place through β-hydroxymethyl-glutaryl-CoA reductase which is a rate-limiting enzyme. Another view is that increased plasma volume in hemolytic anemia of SCD patients, results in the dilution of its constituent lipids as well as lipoproteins. An increase in utilization of cholesterol during the increased erythropoiesis of SCD and abnormalities in liver function along with increased oxidative stress appears to be another causative factor. It was also viewed that enhanced cholesterol concentration per RBC, is linked to lowered levels of cholesterol in patients with SCD (Marzouki and Khoja, 2003). Further it was demonstrated that lower levels of cholesterol, seem to be a result of anemia itself, and not elevated biogenesis of RBC (Westerman et al., 1964).

We found that the HDL concentrations were significantly lower which is similar to observations of previous studies. HDL has been independently associated with cardiovascular risk. Each mg of decrease has been thought to increase the risk by 3–4% (Zibaeenezhad et al., 2017). HDL exhibits a crucial role in risk decreases due to hemolysis and also improved endothelial dysfunction, thereby contributing to improved medical outcomes. Even earlier studies have linked hemolysis with decreased HDL, and inflammation to decreased apolipoprotein A1 levels in SCD. The altered HDL during the course of the disease may turn out to be dysfunctional, resulting in a decreased reverse cholesterol transport (Yalcinkaya et al., 2019). Omega-3 fatty acids have been shown to improve HDL in CVD patients and in our study too, the HDL concentrations increased significantly (Franceschini et al., 1991).

In our study, triglyceride levels were found to be lower initially, which increased after supplementation with omega-3 fatty acids, though earlier reports show inconsistencies in adult patients with increases during VOC crises. Furthermore, as compared to other dietary lipids, triglycerides are mainly found to be dependent on the fasting or non -fasting status during blood collection. Also, the type of fat consumed, and time elapsed in non-fasting patients, can significantly influence the TG levels. In our study, the fasting status of the children was maintained as much as possible.

Decreased triglycerides between the range 70 and 100 mg/dL are suggestive of poor release of fatty acids, endocrine dysfunction, and immune problems. The TG/ HDL ratio appears to be a stronger predictor of cardiovascular problems, than high total cholesterol and LDL/HDL ratios. It is generally observed that people with high triglycerides have the tendency to have low HDL levels. Irrespective of gender, a higher TG/HDL-C ratio causes an increase in the prevalence of hypercholesterolemia, hypertriglyceridemia, and hypertension. This ratio seems to be the best predictor for metabolic syndrome, and acute myocardial infarction. To identify the risk of threat for metabolic syndrome and cardiac risk, a different cutoff ratio is to be applied for both genders as the HDL-C levels are greater in females. Different authors suggest different cutoffs

for adults (2.5 for females and 3.5 for males, while some suggest 3.00 for females and 3.75 for males). The conventional cut offs considering triglyceride value of 150 mg/dL in both males and females and a HDL –C value of 40 mg/dL in males and 50 mg/dL in females was found to be 3.75 in males and 3.00 in females (Silva et al., 2021).

Though routinely analyzed lipid parameters have been associated with the advancement of coronary disease, the ratio of triglycerides to HDL-cholesterol is strongly found concomitant with the extent of the disease. An increase in TG to HDL ratio has been considered a potent predictor of extensive coronary disease. This ratio was also earlier proposed as a precise forecaster of major cardiovascular risk (da Luz et al., 2008).

This TG/HDL ratio acts as an index which is highly predictive of myocardial infarction, more than that of TC/HDL or the LDL/HDL ratio. Another study showed that though TG is a strong predictor of a cardiovascular risk, but TG/ HDL ratio was a more accurate forecaster of enhanced risk of cardiovascular disease (Jeppesen et al., 1998). In our study, though a decrease was observed in TG/ HDL ratio of all patients, only the females of age group 11-16yrs showed a significance. A longer time period may show a clearer picture. Nevertheless, the decrease shows a clear improvement in the lipid status and lowering of predictable cardiovascular risk.

A statistically significant correlation ($P < 0.04$) was found between total cholesterol and hemoglobin concentration in our study which is similar to earlier findings (El-Hazmi et al., 1995).

It has been observed that lipolytic generation of the inflammatory fatty acid arachidonic acid, and other inflammatory molecules results in vascular dysfunction (Boyanovsky and Webb, 2009). Moreover, an unfavorable fatty acid profile has been linked to clinical severity in patients with SCD (Khan et al., 2022; Ren et al., 2006). Although the levels of LDL are low in patients with SCD, the LDL molecule is oxidized easily and also susceptible to endothelium cytotoxicity (Belcher et al., 1999).

The correction to a slightly higher concentration of LDL is observed in all the patients supplemented in our study. A previous study observed increases in LDL on administration of EPA and DHA in higher concentrations to patients with high TG values. It was hypothesized that the rise in LDL, was probably due to an increased LDL particle size by omega-3 fatty acids rather than its number. (Egert et al., 2009).

Earlier studies have shown that in patients with hyperlipidemia, combinations of EPA and DHA reduce TG levels by $\geq$ 30%, along with a simultaneous surge in levels of LDL, whereas only EPA supplementation resulted in a decrease in TG levels without affecting LDL levels (Skulas-Ray et al., 2019).

On consumption, omega 3 fatty acids get incorporated into the cell membrane and cause improvement in its composition and proper functioning, by modulating the bioactive lipid moieties. In fact omega-3 fatty acids act as reservoirs of bioactive lipid mediators. The cell function of regulating the membrane bound proteins, enhancing transport of signaling molecules, controlling inflammatory processes and modulation of transcription factors, is enhanced (Surette, 2008).

5. Conclusions

Omega-3 supplementation was associated with significant increase in lipids biomarkers and hemoglobin concentration, in children with sickle cell disease. Omega3 fatty acids may therefore possibly be used as effective and safe add on supplements during therapy, to reduce the complications accompanying SCD which results from the low lipids values present in SCD.

Recommendations

a. Regular measurement of lipids biomarkers should be done to improve disease management, as they could be a potential predictor of SCD severity.
b. As HbF and serum ferritin play a significant role in the progression of the disease.Therefore a properly structured future study with a control group, incorporating correlations with HbF and ferritin, could give better insights about the role of lipids in SCD.

6. Limitations of the study

The number of patients in our study were few. Our initial findings should be continued by larger well-structured randomized studies with appropriate controls, a proper fasting status, and diet evaluation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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