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RESEARCH ARTICLE

Oxidative biomarkers, trace elements, and other biochemical markers among sickle cell patients receiving omega-3 supplements: case-control study

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Background and aims: Sickle cell anaemia (SCA) is an autosomal recessive haematological disorder in which the gene coding for the beta chain of haemoglobin is mutated. Patients with SCA have higher levels of pro-oxidants such as lipid peroxide and lower levels of antioxidants. There is previous evidence that omega-3 fatty acid supplementation is a safe and effective treatment for SCA as an adjunct therapy alongside conventional treatments, as it is beneficial in decreasing anaemia, vaso-occlusive crises, inflammation, and haemolysis. This study aimed to assess the effect of omega-3 supplementation on the levels of lipid peroxide, trace elements (magnesium, copper, and zinc), and other biochemical markers in sickle cell patients.
Methods: Ninety individuals (4–20 years old) were divided into 4 groups: Group A: 51 patients with SCA on omega 3 supplements, Group B: 22 sickle cell patients not on omega 3 supplementation, Group C: 17 healthy controls, and Group D: forming the patients' group (Group A and Group B combined). Blood samples were collected to measure lipid peroxide, magnesium, copper, zinc levels, and other biochemical markers.
Results: No differences were found between Group A and Group B for all variables except magnesium levels, which were higher in Group B (16.9 ± 7.1 mg/l for Group B and 11.9 ± 7.8 mg/l for Group A, $p < 0.001$). In comparison with Group C, Group D had lower haemoglobin levels ($p < 0.001$) and higher levels of lipid peroxide ($p < 0.001$). Both groups C and D had lower copper levels than the normal range.
Conclusion: No association was found between omega-3 supplementation and the level of the measured biomarkers. The cause of low copper levels in Sudanese paediatric participants should be further investigated.

Introduction

Sickle cell anaemia (SCA) is an autosomal recessive haematological disorder in which the gene coding for the beta chain of haemoglobin is mutated.[1] Sickle cell anaemia affects many ethnic groups worldwide and many tribes in wide geographical areas in Sudan. Recent estimates suggest more than 275 000 affected children are born in Africa every year.[2] Early studies in Sudan concluded that sickle cell disorders are a major health problem in certain parts of the country, particularly the western regions.[3]

Patients with sickle cell anaemia have higher levels of pro-oxidants such as lipid peroxide and lower levels of anti-oxidants such as glutathione peroxidase, superoxide dismutase, and catalase. SCA disease has an increased state of oxidation. When the red blood cell becomes haemolysed, reactive oxygen species are produced, which affect the severity of the disease.[4] Malondialdehyde (MDA) is a product of lipid peroxidation that causes damage to protein and DNA, decreases membrane fluidity, and inactivates membrane-bound enzymes and receptors. All these oxidative changes are accompanied by decreased antioxidant enzyme levels.[5]

Multiple organs are affected by the oxidative stress imbalance seen in SCA. For example, the functional integrity of the kidney is affected by the oxidative damage, leading to tubular glomerular dysfunction, which manifests as high urea and creatinine levels.[6]

Trace elements, e.g. magnesium, zinc, and copper, are required for proper cell function. Sickle cell disease is characterised by disrupted membrane integrity due to fragility, dehydration, and increased production of reactive oxygen species. Consequently, there is a depletion of these trace elements in SCA patients.[7]

Omega-3 polyunsaturated fatty acid (PUFA) is a precursor for eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid (ALA). Lipoxygenase products of the omega-3 fatty acids DHA and EPA are potent anti-inflammatory mediators. In addition, omega-3 fatty acids have antiaggregatory, anti-adhesive, and vasodilatory effects, which are beneficial for sickle cell patients.[8–10]

The omega 3 PUFA effect in patients with SCA has been studied in multiple experimental and clinical studies, where it has been evidenced that omega 3 is beneficial in decreasing anaemia, frequency of blood transfusion, vaso-occlusive crises, coagulopathy, inflammation, and haemolysis.[11–14] It was concluded that omega-3 fatty acid supplementation can be a safe and effective treatment for sickle cell disease as an adjuvant therapy alongside conventional treatments (antimetabolites, analgesics, and antibiotics). This study was designed to determine the effect of omega-3 supplementation on the plasma levels of haemoglobin, lipid peroxide, urea, creatinine, and elemental metals (magnesium, copper, and zinc) in sickle cell patients.

Materials and methods

This retrospective case-control study was conducted at the Paediatrics Referral Clinic of Sickle Cell Anemia at Gaafar Ibnauf Children's Hospital (Khartoum, Sudan) from March to July 2015.

Ninety individuals participated in this study and according to their retrospective history of SCA diagnosis and their history of supplementation with omega 3, they were categorised into four groups as follows: Group A: 51 patients diagnosed with SCA based on haemoglobin electrophoresis (Hb SS) and on omega 3 supplements for at least the last six months. Group B: 22 patients diagnosed with SCA (Hb SS) not on omega-3 supplementation. Group C: 17 healthy children with normal haemoglobin (Hb AA) as controls. Group D: this formed the patients' group, including both Group A and Group B combined. Initially, 10 cc blood samples were collected from the participants in two tubes (EDTA tubes and lithium heparin) for measurement of the biochemical variables.

The patients had already been diagnosed by clinicians in the Paediatrics Referral Clinic of Sickle Cell Anemia. Group A patients were on omega-3 supplements in addition to their conventional therapy. The protocol for management of SCA in Sudan is to initiate continuous omega-3 supplementation at the age of 2 years in addition to conventional therapy. However, this was considered a costly supplement, and the hospitals were not supplying it to the patients free of charge. Patients who were not able to afford the supplement formed Group B of the study.

Patients included in this study were between 4 and 20 years of age. Omega 3 supplement dosage (number of capsules) taken by Group A was prescribed according to the patient's weight (25 mg/kg bodyweight). The omega-3 capsule contained 277.8 mg DHA and 39.0 mg EPA.[15] All patients were on folic acid, multivitamin supplements, and some on prophylactic penicillin and hydroxyurea. Controls were selected from the community who were comparable to the patient group in terms of age, sex ratio, and socioeconomic class.

This research has been ethically approved by the Ethical Committee of the Faculty of Medicine, University of Khartoum. It was conducted in compliance with the ethical standards of the Ethical Committee of the Faculty of Medicine, University of Khartoum on human subjects as well as with the Helsinki Declaration. The study was fully explained to the parents/guardians of the participants, and written informed consent was obtained.

Table 1. Comparison of the different variables between Group A: Omega 3-supplemented and Group B: non-supplemented patient groups.

Measured Variables	Group A Omega 3 supplemented (n = 50) Mean ± SD	Group B Non-omega 3 supplemented (n = 23) Mean ± SD	p value
Age	10.8 ± 4.1	10.7 ± 4.5	0.93
Haemoglobin (g/dl)	7.2 ± 1.2	7.1 ± 0.8	0.69
Lipid peroxide (nmol/l)	9.8 ± 9.1	10.1 ± 8.9	0.89
Urea (mg/dl)	25 ± 10.4	21.3 ± 18.6	0.29
Creatinine (mg/dl)	0.62 ± 0.3	0.47 ± 0.4	0.07
Magnesium (mg/l) Normal range: 16–23 mg/L	7.4 ± 3.7	11.9 ± 7.8	**0.001**
Zinc(mg/l) Normal range: 0.5–1.2 mg/l	0.16 ± 0.87	0.18 ± 0.10	0.41
Copper(mg/l) Normal range: 0.81–1.35 mg/L	0.42 ± 0.21	0.51 ± 0.16	0.08

The blood samples were centrifuged, and plasma was extracted and stored at −20°C. Haemoglobin level was measured by a haematology machine analyser (Sysmex Corp, Kobe, Japan), while lipid peroxide was analysed using a BIODIAGNOSTIC kit (Cairo, Egypt), and the product was measured using spectrophotometry.[16] Urea and creatinine were measured using standard protein methods by Jaffe kits (MDSS GmbH, Hanover, Germany). A Buck Scientific 210/211VGP Atomic Absorption Spectrophotometer (2005; Buck scientific Inc, East Norwalk, CT, USA) was used to measure trace element levels following analytical Methods for Atomic Absorption Spectroscopy, Manual Part No. 0303-0152 D, September 1996.[17]

IBM SPSS Statistics (V.20.0, IBM Corp, Armonk, NY, USA, 2010) was used for data analysis. Results were expressed as the mean ± SD. Comparison between two independent group means was performed using Student's t-test; the p-values reported were two-tailed with 95% confidence intervals of the differences in the means. A p-value of 0.05 was considered significant.

Results

The study included 90 participants with a 2:1 female:male ratio (60:30) who had been recruited and classified into four groups as mentioned in the Methods section.

Comparison of the biochemical variables between the omega-3 supplemented and non-supplemented groups

First, the biochemical variables were compared between Group A and Group B as presented in Table 1. The mean haemoglobin level in Group A was 7.2 ± 1.2 g/dl and in Group B 7.1 ± 0.8 g/dl. There was no significant difference between the two groups ($p = 0.69$). Regarding lipid peroxide, it was found that the mean level in Group A was 9.8 ± 9.1 nmol/l and in Group B 10.1 ± 8.9 nmol/l, and there was no significant difference between the two groups ($p = 0.89$). Blood urea concentration was found to be 25 ± 10.4 mg/dl in Group A and 21.3 ± 18.6 mg/dl in Group B, with no significant difference ($p = 0.29$). Creatinine level was 0.62 ± 0.3 mg/dl in Group A, and 0.47 ± 0.4 mg/dl in Group B. There was an insignificant difference between the compared groups. The magnesium level was found to be 7.4 ± 3.7 mg/dl in Group A and 11.9 ± 7.8 mg/dl in Group B. Group B had significantly higher magnesium levels than Group A ($p < 0.001$). No statistical difference was noted when comparing the zinc levels (0.16 ± 0.87 mg/dl in Group A and 0.18 ± 0.10 mg/dl in Group B, $p = 0.41$). The copper level in Group A was 0.42 ± 0.21 mg/l and 0.51 ± 0.16 mg/l in Group B, and the difference between the two groups was not significant, although the two groups had lower copper levels than the normal range (0.81–1.35 mg/l).

Comparison of the biochemical variables between patients and control groups

Next, Group D was compared with Group C (Table 2). Group D had significantly lower haemoglobin levels (7.1 ± 1.1 and 12.4 ± 1.3 g/dL, $p < 0.001$) and higher levels of lipid peroxide (9.9 ± 9.0 and 1.41 ± 1.7, $p < 0.001$) than Group C. No differences were noticed in the levels of urea and creatinine between the two

groups. When comparing the trace elements levels between the two groups, Group D had both lower magnesium (8.7 ± 5.6 for Group D, 16.9 ± 7.1 mg/l for Group C, $p < 0.001$, normal range: 16–23 mg/l) and zinc levels (0.16 ± 0.1 for Group D, 0.62 ± 0.23 mg/l for Group C, $p < 0.001$, normal range: 0.5–1.2 mg/l). However, both Group D and Group C had lower than normal copper levels (0.45 ± 0.2 for Group D, 0.45 ± 0.15 for Group C, normal range is 0.81–1.35 mg/l) with no significant differences between them (Table 2).

Discussion

This study was designed to discover the effect of omega-3 PUFA supplementation on the level of some biochemical markers among patients with SCA.

Haemoglobin level was found to be significantly lower among patients compared with controls, which is explainable by the ongoing haemolysis of red blood cells as part of the pathology of the disease.[18] However, in comparison with the non-supplemented group, the supplemented group had higher haemoglobin levels, but the difference was insignificant, and no association was found between haemoglobin level and the supplementation of omega-3. A pilot African study found no difference in haemoglobin levels between pre- and post-supplementation periods,[19] which contradicts a previous placebo-controlled study that established a positive correlation between them, with rising haemoglobin levels after supplementation.[20] Another recent study in the Middle East has also proved the positive effect of omega-3 on haemoglobin concentration.[13] Sickled RBCs have an abnormal cell membrane due to disruption of the fatty acid composition, i.e. a high ratio of arachidonic acid, which is pro-inflammatory to anti-inflammatory DHA and EPA. Supplementation with omega-3 fatty acids helps to restore the normal fatty acid composition and decreases the rate of haemolysis.[21] The similar haemoglobin levels seen in the supplemented and non-supplemented groups in the current study might be explained by the close follow-up and regular blood transfusion of the patients by the treating team.

Table 2: Comparison of means of measured variables in Group D: Patients (Both supplemented and non-supplemented) and Group C: control group.

Measured variables	Group D Patients group (both supplemented and non-supplemented) (n = 73) Mean ± SD	Group C Control group (n = 17) Mean ± SD	p value
Age	10.7 ± 4.2	7.4 ± 2.5	**0.002**
Haemoglobin (g/dl)	7.1 ± 1.1	12.4 ± 1.3	**<0.001**
Lipid peroxide (nmol/l)	9.9 ± 9.0	1.41 ± 1.7	**<0.001**
Urea (mg/dl)	23.9 ± 13.5	19.2 ± 6.4	0.18
Creatinine (mg/dl)	0.57 ± .32	0.59 ± 0.2	0.81
Magnesium (mg/l) Normal range: 16–23 mg/L	8.7 ± 5.6	16.9 ± 7.1	**<0.001**
Zinc(mg/l) Normal range: 0.5–1.2 mg/l	0.16 ± 0.1	0.62 ± 0.23	**<0.001**
Copper(mg/l) Normal range: 0.81–1.35 mg/L	0.45 ± 0.2	0.45 ± 0.15	0.86

In our study, lipid peroxide (malondialdehyde) was found to be raised significantly among patients (both supplemented and non-supplemented) compared with controls, which agreed with a study that showed a raised level of MDA among adult patients with SCA along with other inflammatory biomarkers, e.g. C-reactive protein and fibrinogen.[22] It is known that sickled RBCs have higher rates of autoxidation than normal RBCs, which produce high levels of lipid peroxides e.g. MDA and superoxides.[23] However, there was no significant difference in MDA level in the supplemented group compared with the non-supplemented group, and there was no association found between supplementation of omega-3 PUFA and MDA level. The effect of omega-3 PUFA on oxidative status has been controversial. One study in adult Wistar strain rats exposed to an atherogenic diet reported that omega-3 supplementation led to increased levels of reactive oxygen species, which worsened lipid peroxidation, and they recommended the addition of antioxidants to the omega-3 supplementation to prevent the oxidative insult.[24] In comparison, many studies have found a decreasing impact on oxidative stress.[11,25,26] DHA prevents atherosclerosis by enhancing the monocytes' resistance to apoptosis when exposed to oxidised LDL and by promoting the production of the vasoactive biomolecule nitric oxide.[27,28] Furthermore, it is known that omega-3 supplementation has a free radical scavenger effect, which decreases the overall oxidative stress and lowers the immune dysfunction seen in sickle cell patients. This contradictory effect of omega-3 on oxidative stress might be explained by the fact that the protective effect of omega-3 is dose-dependent, with high omega-3 consumption being associated with higher rather than lower oxidative stress.[29]

Urea and creatinine levels were not different between the patients and control groups, which contradicts a study in which both urea and creatinine were lower among sickle cell patients compared with the control group.[30] In addition, an earlier study in Sudan reported low urea levels among patients with SCA.[31] The low urea levels seen in sickle cell patients were attributed to possible liver dysfunction, and the low creatinine to low body muscle mass and dietary insufficiency, which is expected to be seen in a chronic debilitating disease such as SCA.

Finally, trace element measurements revealed that Group D, comprising SCA patients, had lower serum magnesium and zinc levels than the healthy control group. The cause of magnesium (Mg) deficiency in sickle cell patients is increased activity of the erythrocyte Mn/Mg exchanger that promotes Mg efflux.[32] Erythrocyte Mg deficiency contributes to erythrocyte dehydration and potassium loss, and so mediates sickling. Two previous studies have supported the finding that sickle cell patients have low zinc levels.[7,33] The low levels of zinc seen in sickle cell patients have been attributed to continuous haemolysis, loss of zinc in urine, and an adverse effect of the intake of hydroxyurea. Zinc is an antioxidant that inhibits lipid peroxidation in the RBC and protects against oxidative stress and its deficiency manifests as growth retardation, hypogonadism, hyperammonemia, and impaired cell-mediated immunity.

Copper levels were low in both patients and the control groups in this study. This study is the first to report low copper levels in the Sudanese control group. Previous studies on the Sudanese population did not reveal low copper levels in the normal, non-diseased children.[34,35] The low levels seen in this study could be associated with nutritional deficiencies. Copper deficiency is

complicated by microcytic anaemia, as it is essential for haemoglobin production.[36] However, multiple other studies have found that sickle cell patients had higher levels of copper than the control groups.[37–39] The previous finding can be explained by the reciprocal relationship between zinc and copper, and by the increased level of production of ceruloplasmin due to the inflammatory process seen in sickle cell disease.

The low levels of magnesium, zinc, and copper seen in sickle cell patients in this study can be explained by nutritional deficiency in these patients, especially in families with low socioeconomic status. Although all patients were prescribed multivitamin supplements, compliance with the supplements cannot be guaranteed in poor and non-educated families. Sickle cell disease patients frequently report decreased appetite due to multiple factors, including chronic inflammatory status, painful crises, and frequent hospitalisation. The deficiency of these micronutrients has a significant impact on disease severity.

Supplementation of sickle cell patients with omega-3 fatty acids in addition to their conventional treatment was a novel practice at the time of the research, as other researchers and many pharmaceutical companies highlighted its efficacy. This is the first study to look for the effect of omega-3 on trace elements in SCA disease. The effect of omega-3 on trace elements has rarely been studied in other chronic diseases. Omega-3 supplementation was found to increase magnesium levels in patients with fibromyalgia[40] and the deficiency of omega-3 was found to lead to dysregulation of zinc metabolism in Alzheimer's disease.[41]

This study has some limitations. One sample was taken at the time of the study from the participants, although a comparison between pre- and post-supplementation would be more appropriate to elucidate any differences and to control for possible confounding factors. Another limitation is that the nutritional and socioeconomic status, two factors that might have affected the results, were not assessed in this study. As all patients (both supplemented and non-supplemented) were taking multivitamins and folic acid, we recommend assessing the effect of dose and duration of the multivitamins on the lipid peroxides and trace elements in future similar studies.

In this study, the supplementation of omega-3 had no effect on the levels of lipid peroxides and the trace elements magnesium, zinc, and copper in sickle cell patients. This is the first study to look for the effect of omega-3 on lipid peroxide and trace elements levels in SCA disease as the effect of omega-3 on trace elements has rarely been studied in other diseases.[40,41] More studies on omega-3 use among patients with sickle cell anaemia should be encouraged with the recruitment of a larger number of participants from multiple centres.

Conclusion

No association had been found between omega-3 supplementation and the level of the measured biomarkers. The cause of low copper levels in Sudanese paediatric participants should be further investigated.

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Informed consent – The parents/guardians of both patients and control group members were consulted concerning their willingness and approval to participate in the study and an informed written consent was taken. All data in this study are confidential.

Author contributions – ASO and AOM designed the research and wrote the draft. ASO recruited the participants, collected the data, and undertook the laboratory work. ASO and SG did statistical analysis and interpretation of results. AOM and SG critically reviewed the manuscript.

Institutional review board approval – This research has been ethically approved by the Ethical Committee of the Faculty of Medicine, University of Khartoum.

Ethical compliance with human/animal study – This study was conducted in compliance with the ethical standards of the Ethical Committee of the Faculty of Medicine, University of Khartoum on human subjects as well as with the Helsinki Declaration.

Data availability – The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

List of abbreviations – SCA: sickle cell anaemia, PUFA: polyunsaturated fatty acid, HbS: haemoglobin S, Hb: haemoglobin, EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid, MDA: malondialdehyde.

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