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Impact of Omega-3 Deficiency on Inflammation and Hemolysis in Sickle Cell Anemia Patients in Basrah, Iraq

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ABSTRACT

Background: Although the benefits of omega-3 fatty acids in inflammatory and hemolytic disorders other than sickle cell anemia (SCA) are well established, their role is underexplored in this population. This study aimed to investigate the impact of omega-3 fatty acid deficiency on clinical outcomes, including inflammation, hemolysis, and vaso-occlusive crisis (VOC) frequency in patients with SCA.

Methods: A cross-sectional study was conducted among 110 SCA patients in Iraq. Participants were categorized as omega-3 deficient (<3% total plasma fatty acids) or sufficient (≥3% total plasma fatty acids) based on plasma level determined by gas chromatography-mass spectrometry (GC-MS). Clinical data, including VOC frequency, inflammatory biomarkers of interleukin-6 (IL-6), tumor necrosing factor-alpha (TNF-α) and C-reactive protein (CRP), and hemolysis markers of lactate dehydrogenase (LDH) and hemoglobin were analyzed.

Results: Omega-3 deficient patients (n=62) had significantly higher levels of inflammatory biomarkers compared to omega-3 sufficient patients (n=48), including IL-6 (15.1±3.2 vs. 9.5±2.7 pg/mL, $p<0.001$) and TNF-α (21.3±4.1 vs. 12.4±3.5 pg/mL, $p<0.001$). Hemolysis markers, such as LDH (588±72 vs. 465±58 U/L, $p<0.001$), were also elevated in the deficient group. The frequency of VOCs was significantly higher among omega-3 deficient patients (3.4±1.3 vs. 2.1±1.1 episodes/year, $p<0.001$). Multivariable regression analysis identified omega-3 level as an independent predictor of VOC frequency (β=-0.384, $p<0.001$).

Conclusion: Omega-3 deficiency was shown to be associated with an increased inflammation, exacerbated hemolysis, and a higher VOC frequency in SCA patients suggesting that omega-3 supplementation may be a valuable adjunctive therapy for managing SCA.

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Introduction

Ferropenia and consequent iron deficiency anemia (IDA), β-thalassemia, glucose 6-phosphate dehydrogenase (G6PD) deficiency and sickle cell anemia (SCA) are the main common hematological problems in many Middle East countries (1-4). SCA is considered to be an autosomal recessive hereditary hemoglobinopathy and develops from the abnormal properties of hemoglobin S. Low partial pressure of oxygen initiates hemoglobin

S polymerization, deformation, and leads vaso-occlusive episodes (VOEs) to start triggering of the hemolysis event (1, 5). Its chronic nature provides inflammatory events with great damage to the endothelium characterized with oxidative stress processes that can significantly account for huge morbidities, as well as mortality in SCA patients (6).

Of particular interest in SCA is the role of omega-3 fatty acids in mitigating these pathological mechanisms. Omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are two classes of essential polyunsaturated fatty acids (PUFAs) that have critical roles in the regulation of inflammation and immune function via their impacts on cardiovascular health (7, 8). Omega-3 PUFAs have demonstrated potential in reducing inflammatory cytokine production, improving endothelial function, and decreasing platelet aggregation-all key factors implicated in the complications of SCA (9, 10).

Indeed, there is an emerging body of evidence that omega-3 deficiency can be a pro-inflammatory process and potentially worsen the course of SCA. Low level of omega-3 was shown to be associated with increased pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) which are commonly elevated in patients with SCA (11). Besides that, omega-3 deficiency can lead to impairment of inflammation resolution that is a very crucial mechanism of handling chronic diseases like SCA; where the patients suffer with recurrence of VOEs and chronic oxidative damage (12, 13). Additionally, omega-3 PUFAs play a crucial role in membrane fluidity and deformability, which are compromised in sickled red blood cells (RBCs) (14). By restoring membrane integrity, omega-3 supplementation can improve RBC functionality and reduce hemolysis, thus offering potential therapeutic benefits (15, 16). As there are very limited researches in literature directly examining the deficiency of omega-3 in SCA and the deficiency in omega-3 can lead to worsening of the vascular complication associated with SCA, underlining the fact that targeted investigation into this should be conducted; therefore, his study was undertaken to determine the impact of omega-3 deficiency on inflammation and hemolysis in sickle cell anemia patients in Basrah, Iraq.

Materials and Methods

This study was a cross-sectional design to determine the association of omega-3 deficiency with clinical outcomes among SCA patients. It was considered efficient to study the association of different variables at one point in time and thus allows for thorough analysis of omega-3 level and the association with markers affecting the disease severity, inflammation, and lipid profile. The research was carried out in Basrah, Iraq through an already existing network of hematology clinics and hospitals that treated SCA patients. The inclusion criteria were (i) Patients aged 18-45 years diagnosed with SCA based on hemoglobin electrophoresis results; (ii) Having a stable disease status defined as no acute vaso-occlusive crises (VOCs) in the last four weeks and (iii) absence of any history of omega-3 supplementation in the past six months. The exclusion criteria were not to be pregnant or breastfeeding women; absence of any chronic inflammatory or autoimmune disorders unrelated to SCA; Receipt of treatments affecting lipid metabolism, such as statins or corticosteroids and renal or hepatic dysfunction determined by medical records or laboratory tests.

To determine the appropriate sample size, a power analysis was conducted using G* power software. Assuming a medium effect size (Cohen's: f=0.25, f=0.25, f=0.25) with a power of 0.80 and an alpha level of 0.05, the minimum required sample size for detecting differences in omega-3 level and the association with clinical outcomes was calculated to be 90 participants. To account for potential dropouts or incomplete data, 110 participants were recruited. All participants provided written consent, and the study followed the guidelines outlined in the declaration of Helsinki principles. Participants were made aware of their freedom to withdraw from the study at any point without facing any negative repercussions.

The level of omega-3 was determined using gas chromatography-mass spectrometry (GC-MS). Blood samples were taken after a night of fasting to guarantee uniformity. The researchers measured the levels of EPA and DHA in the plasma, and then determined the total omega-3 content. Severity of SCA was evaluated using (i) Frequency of VOCs as self-reported VOC episodes requiring medical intervention in the past year were recorded. (ii) Markers of hemolysis by measuring the serum lactate dehydrogenase (LDH) and indirect bilirubin levels using an automated biochemical analyzer. (iii) Complete blood count (CBC) by assessing hemoglobin level, reticulocyte count, and mean corpuscular volume (MCV). (iv) Evaluation of inflammatory biomarkers including IL-6, TNF-α and C-reactive protein (CRP) utilizing enzyme-linked immunosorbent assay (ELISA) kits. All assays were performed in triplicate to ensure accuracy.

Results

The participant demographics were presented in Table 1. A total of 110 participants were enrolled in the study, including 58 males (52.7%) and 52 females (47.3%). The mean age of participants was 30.2±8.5 years, with a mean body mass index (BMI) of 23.5±4.2 kg/m². Participants were stratified into two groups based on their plasma omega-3 level as omega-3 deficient (<3% total plasma fatty acids) and omega-3 sufficient (≥3% total plasma fatty acids). Patients with omega-3 deficiency demonstrated worse clinical outcomes, including higher VOC frequency, elevated markers of inflammation, and greater hemolysis markers when compared to those with sufficient omega-3 level. The omega-3 deficient group reported significantly higher annual VOC frequency in comparison to the sufficient group, suggesting a potential association between omega-3 level and VOC incidence.

Omega-3-deficient subjects had significantly higher levels of inflammatory markers (IL-6, TNF-α, CRP) and hemolysis markers (LDH), with lower hemoglobin levels that can be the indicative of a protective role for omega-3 in the inflammation and hemolytic processes of SCA. The correlations between omega-3 levels, inflammatory markers, and clinical outcomes were evaluated using Pearson's correlation coefficients. Omega-3 level was inversely related to the levels of inflammatory markers and VOC frequency, directly related to hemoglobin levels. These findings support the hypothesis that omega-3 deficiency exacerbates inflammation and

Table 1: Participants' demographic characteristics.

Variable	Total (n=110)	Omega-3 deficient (n=62)	Omega-3 sufficient (n=48)	*P* value
Age (Years)	30.2±8.5	29.8±8.7	30.6±8.3	0.542
Male, n (%)	58 (52.7%)	34 (54.8%)	24 (50%)	0.643
BMI (kg/m²)	23.5±4.2	24.2±4.3	22.8±4.1	0.131
Annual VOC Frequency	2.8±1.4	3.4±1.3	2.1±1.1	<0.001***

BMI: Body mass index; n: Number; VOC: Vaso-occlusive crisis.

Table 2: Comparison of clinical data by omega-3 status.

Variable	Omega-3 deficient	Omega-3 sufficient	*P* value
IL-6 (pg/mL)	15.1±3.2	9.5±2.7	<0.001***
TNF-α (pg/mL)	21.3±4.1	12.4±3.5	<0.001***
CRP (mg/L)	8.5±2.3	4.2±1.8	<0.001***
Hemoglobin (g/dL)	7.9±1.3	9.2±1.1	<0.001***
LDH (U/L)	588±72	465±58	<0.001***
Total Cholesterol (mg/dL)	172.4±28.5	151.7±25.3	0.002**

CRP: C-reactive protein; IL-6: Interleukin-6; LDH: Lactate dehydrogenase; TNF- α: Tumor necrosing factor-alpha.

Table 3: Correlation between omega-3 levels and clinical variables.

Variable	R value	*P* value
VOC Frequency	-0.568	<0.001***
IL-6 (pg/mL)	-0.621	<0.001***
TNF-α (pg/mL)	-0.532	<0.001***
CRP (mg/L)	-0.487	<0.001***
Hemoglobin (g/dL)	+0.471	<0.001***
LDH (U/L)	-0.451	<0.001***

CRP: C-reactive protein; IL-6: Interleukin-6; LDH: Lactate dehydrogenase; TNF- α: Tumor necrosing factor-alpha; VOC: Vaso-occlusive crisis.

Table 4: Regression model for predicting VOC frequency.

Variable	Beta coefficient (β)	Standard error (SE)	*P* value
Age (Years)	+0.012	0.008	0.141
Male (ref: Female)	+0.138	0.124	0.271
BMI (kg/m²)	+0.057	0.028	0.041*
Omega-3 level (%)	-0.384	0.042	<0.001***

BMI: Body mass index.

hemolysis in SCA patients. We used multivariable linear regression analysis, adjusted for age, sex, BMI, and omega-3, to find the independent predictors of VOC frequency. This would then imply that the level of Omega-3 was an independent factor related to VOC frequency after adjustment. It suggests possible benefits of using Omega-3 supplements with relevance in SCA patients (Table 2-4).

These benefits possibly concern SCA complications. Omega-3-deficient patients showed a greater VOC frequency than patients with a sufficiency, coupled with a high level of worse inflammatory profiles along with increased hemolysis. There were significant correlations between the levels of omega-3 with inflammatory markers (IL-6, TNF-α, CRP), hemolysis marker of LDH, and hemoglobin. Omega-3 level emerged as an independent predictor of frequency of VOC in SCA patients (Table 2-4).

Discussion

Omega-3 fatty acids are PUFAs with several health benefits that play a critical role in many cellular activities, such as cellular signaling pathways, cell-to-cell communication and maintaining cell membrane integrity. They have anti-inflammatory, anti-depressant, anti-cancer, autophagy, and lipid-lowering properties (17, 18). Our findings emphasized that the deficiency in omega-3 fatty acid was significantly correlated with the clinical severity of SCA. The participants with lower level of omega-3 fatty acids had significantly an increased frequencies of VOC, a rise in inflammatory markers, and poor hemolysis parameters. These findings are in agreement with the literature on anti-inflammatory and membrane-stabilizing properties of omega-3 fatty acids and provide evidences for the possible role of omega-3 fatty acids in the prevention of complications in SCA (10, 19).

In our study, among patients with omega-3 deficiency, levels of IL-6, TNF-α, and CRP were higher revealing well-recognized markers of systemic inflammation. This finding is in agreement with the known role of omega-3 fatty acids in modulating inflammatory pathways. Omega-3 fatty acids, in particular, are precursors of resolvins and protectins, while these bioactive lipids exert activities attributed to the resolution of inflammation-defective processes in chronic inflammatory conditions, including SCA (20, 21). Additionally, an extremely strong negative relation of omega-3 with both VOC frequency and inflammatory markers was demonstrated. This may indicate that a deficiency in omega-3 could worsen the inflammatory setting of SCA and increase the risk of VOC and other complications. Furthermore, the positive relationship between omega-3 level with hemoglobin concentration and the negative correlation with LDH point out the potential role of omega-3 fatty acids in improvement of RBC stability and in reducing hemolysis. Taken together, these findings point toward the hypothesis that omega-3 fatty acids that may play a protective role in SCA by preventing both inflammatory and hemolytic complications (12, 13, 22).

The biological mechanisms whereby deficiency in omega-3 relates to poor prognosis in SCA can be explained by its impact on cellular and molecular processes. Firstly, omega-3 fatty acids are involved in maintaining structural integrity and fluidity of RBC membranes. The changes in the biophysical properties of sickled RBCs, as present in SCA, would promote hemolysis and vaso-occlusion. Omega-3 fatty acids incorporated into phospholipid bilayers would increase membrane deformability and decrease the likelihood of RBC aggregation and adhesion to the vascular endothelium. This effect might be the one accounting for the observed association of increased levels of omega-3 fatty acids with lower markers of hemolysis (16, 23, 24).

Thus, anti-inflammatory activities of omega-3 fatty acids provide importance in SCA. As an innate immunity-related continuous process, chronic inflammation increases cytokine production such as IL-6 and TNF-α in SCA. Omega-3 fatty acids play their role opposite to this inflammation through the interruption of NF-κB signaling-a pivotal pathway to produce pro-inflammatory cytokines. In addition, omega-3 can promote resolution of inflammation through enhancing macrophage phagocytosis of apoptotic cells and debris. The combination of reducing inflammation and promoting resolution may explain the substantially decreased inflammatory burden observed in omega-3-sufficient participants (11, 14, 22).

Lastly, the role of omega-3 fatty acids in cardiovascular health is very well documented. With such a high prevalence of vascular complications in patients with SCA, including pulmonary hypertension and stroke, there is enormous scope for improvement through modulation of endothelial function, reduction of oxidative stress, and attenuation of platelet aggregation in mitigating these vascular complications that form the bedrock of the morbidity and mortality seen in SCA (23, 24). A significant link between the deficiency and bad clinical outcomes in our study implies that supplementation with omega-3 (EPA and DHA) through food sources such as fatty fish or pharmaceutical grades of omega-3 could be an important adjunct therapy in this condition to prevent the VOCs, reduce systemic inflammation,

and ameliorate hemolysis parameters (25).

Furthermore, the relatively low cost and favorable safety profile of omega-3 fatty acids make it an accessible supplement for patients in resource-limited settings such as Iraq; where prevalence of SCA is quite high. Supplementing with omega-3 can be an adjunctive therapy that may complement more conventional treatments such as hydroxyurea and blood transfusions. It was shown that omega-3 supplementation might augment hydroxyurea by inhibiting the inflammation process, making the RBC membrane more stable and therefore reducing the complications associated with the disease (26).

Our study showed that SCA patients with omega-3 deficiency had highly increased levels of inflammatory biomarkers, including IL-6 and TNF-α, and increased VOCs. These findings agree with the work of Kalish *et al.* who found that omega-3 fatty acids lowered systemic inflammation and endothelial activation in a transgenic mouse model of SCA. Omega-3 supplementation normalized the omega-6/omega-3 fatty acid ratio, reduced neutrophil count, and lowered markers of endothelial dysfunction, offering a mechanistic explanation for the observed anti-inflammatory effects (10). Similarly, Daak *et al.* reported that omega-3 fatty acids reduced the NF-κB gene expression and lowered the levels of integrin in SCA patients (22). The anti-inflammatory action of omega-3 fatty acids in agreement with our findings was demonstrated that confirms the status of omega-3 as an anti-inflammatory agent in SCA patients (23).

Our study portrayed a patient profile that had features of omega-3 deficiency level elevated by hemolysis markers, especially LDH and reduced hemoglobin. This aspect aligns with It was shown that supplementation by omega-3 fatty acids affected RBC flexibility as well as decreasing the level of irreversibly sickled red blood cells in the mouse SCA model. DHA supplementation was exhibited to lead to a significant improvement in RBC deformability, which is critical in reducing hemolysis and vaso-occlusion (13, 14, 16, 25). In addition, Valenti *et al.* observed that omega-3 fatty acids enhanced the rheological properties of RBCs and diminished markers of oxidative stress in sickle cell mice. These findings are in agreement with our observations and suggest that omega-3 fatty acids are important in maintaining RBC stability and reducing complications associated with hemolysis (12, 16, 27).

In our study, the frequency of VOCs was significantly declined in omega-3 sufficient patients. A meta-analysis conducted before showed a similar pattern of omega-3 supplementation with the reduction in the frequency of VOCs and hospitalizations for acute chest syndrome among SCA patients (13). According to other reports, It was due to anti-inflammatory and anti-thrombotic properties of omega-3 fatty acids (20, 28, 29). In another RCT study, It was shown that omega-3 supplementation could reduce the number of painful crises and improve the lipid profile of pediatric SCA patients (27). These observations are in consonance with ours and emphasize the therapeutic role of omega-3 fatty acids in the reduction of VOC-related morbidity (29, 30).

Conclusion

Our study showed that omega-3 deficiency was associated with increased inflammation, higher rates of hemolysis, and a greater frequency of VOCs. Therefore, omega-3 supplementation can be an adjuvant therapy in SCA, especially in regions with high disease burden where resources are limited. Further research is needed in larger clinical trials regarding optimal dosing, long-term safety, and efficacy in diverse populations of SCA.

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Authors' Contribution

Qutaiba A Qasim contributed to concept, design, literature search, experimental study, manuscript preparation, manuscript editing and manuscript review.

Conflict of Interest

The authors declare no conflict of interest.

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