Omega- 3 fatty acids are potential therapy for patients with sickle cell disease

We have read with interest the excellent review on sickle cell disease recently published in your Journal Nature Review – Disease Primers (Kato et al. 2018; 4:18019) The review succinctly highlights the recent advances in the molecular pathology of sickle disease, medical management options, and future challenges. However, the review failed to underscore the critical role of blood cell membrane lipid abnormality in the pathogenesis of the disease, as well as the therapeutic potential of long chain omega-3 fatty acids demonstrated in pilot and randomized studies [1-5].

The authors have stated, "HbS polymerization directly or indirectly alters the typical lipid bilayer and proteins of the erythrocyte membrane". They did not, however, mention that red and white blood cells and platelets of patients with SCD have an abnormal membrane fatty acid composition, characterized by decreased levels of docosahexaenoic (DHA, 22:6ω3) and eicosapentaenoic (EPA, 20:5ω3) acids, and a concomitant increase in arachidonic (AA, 20:4ω6) acid [4, 6, 7]. These findings suggest that membrane lipid perturbation and its manifestations, including the exposure of phosphatidyl serine on the exterior of red blood cell membranes and the propensity of erythrocytes, white blood cells, and platelets to adhere and aggregate is fundamental to sickle cell pathology.

Tomer et al [1], reported a lower frequency of pain episodes in SCD patients treated with omega-3 fatty acids. Subsequent to the aforementioned pilot study, Daak et al [5] conducted a large single center randomized, double-blind, placebo-controlled trial with omega-3 fatty acids in patients with homozygous sickle cell disease. The annual vaso-occlusive crisis rate (VOC), number of hospitalization days for VOC, and rate of hospitalizations were significantly lower in the omega-3 group than in subjects who received placebo capsules. We have recently concluded a multi-center (n=11) phase 2 randomized, double-blind, placebo-controlled, parallel-group, dose-finding trial (SCOT) in the United States. Our preliminary data, consistent with previous findings, reveals a greater than 55% reduction in clinical sickle cell crises in patients treated with DHA. A detailed protocol of the SCOT trial is provided on the ClinicalTrials.gov website (https://clinicaltrials.gov/ct2/show/NCT02973360).

These clinical studies provide evidence that omega-3 fatty acids are effective and safe treatment options for patients with sickle cell disease. The specific mechanisms through which these fatty acids ameliorate vaso-occlusive crises is yet to be elucidated. Nevertheless, omega-3 fatty acids and their active metabolites have well-substantiated pleiotropic biological actions - anti-inflammatory, inflammation resolving, anti-adhesion, anti-aggregation, vasodilatory and antioxidant [8-11]. In addition, there is evidence that membrane fatty acid abnormality, red blood rheological abnormalities, inflammation and hemolysis are ameliorated by treatment with DHA and EPA[11-14].

In the last 20 years, only one drug has been approved for SCD and most of the experimental medications have failed to live up to their earlier promise. This is to be expected because of the complex nature of SCD pathophysiology. Hence, multimodal therapy or a single drug with multiple mechanisms of action may be necessary to achieve clinical effectiveness[15, 16]. The multipronged biological and pleiotropic effects of omega-3 fatty acids make them a novel therapeutic option for patients with SCD.

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