DIETARY OMEGA-3 POLYUNSATURATED FATTY-ACID SUPPLEMENTATION REDUCES PAINFUL DIABETIC NEUROPATHY AND UPREGULATES NEUROPROTECTIVE CELLULAR PATHWAYS IN LATINOS WITH TYPE 2 DIABETES

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Background: Omega-3 polyunsaturated fatty acids (PUFAs) are proposed to improve chronic neuroinflammatory diseases in peripheral and central nervous systems. For instance, docosahexaenoic acid (DHA) protects nerve cells from noxious stimuli in vitro and in vivo. Recent reports link PUFA supplementation to improving painful diabetic neuropathy (pDN) symptoms. Still, the cellular mechanisms responsible for this therapeutic effect are not well understood. The objective of this study is to 1) determine whether dietary supplementation with PUFAs reduces neuropathic pain symptoms in Mexican-Americans with type 2 diabetes mellitus (T2DM) and 2) identify distinct cellular pathways elicited by dietary PUFA supplementation in patients with T2DM affected by pDN.

Methods: Forty volunteers diagnosed with T2DM were enrolled in the “En Balance-PLUS” diabetes education study. The volunteers participated in weekly lifestyle/nutrition education and daily supplementation with 1000 mg DHA and 200 mg eicosapentaenoic acid. The Short-Form McGill Pain Questionnaire validated clinical determination of baseline and post-intervention pain complaints. Laboratory and untargeted metabolomics analyses were conducted using blood plasma collected at baseline and after three months of participation in the dietary regimen. The metabolomics data were analyzed using random forest, hierarchical clustering, ingenuity pathway analysis, and metabolic pathway mapping.

Results: A total of 26 participants self-reported neuropathic pain symptoms at baseline. After three months of omega-3 PUFA supplementation, participants reported significant improvement in SF-MPQ scores. Untargeted metabolomic analysis revealed that participants in the moderate–high SF-MPQ group had the highest relative plasma sphingosine levels at baseline compared to the low SF-MPQ group and the no-pain group. Omega-3 PUFA supplementation increased plasma DHA and reduced plasma sphingosine levels in participants reporting neuropathic pain symptoms. Increased plasma DHA levels significantly correlated with improved SF-MPQ sensory scores. However, improved SF-MPQ scores did not correlate with clinical/laboratory parameters. Also, the data show that metabolites involved in oxidative stress and glutathione production shifted significantly to a more anti-inflammatory state post supplementation.

Conclusion: The significant findings of this study are as follows. Omega-3 PUFA supplementation is associated with a significant reduction in self-reported neuropathic pain symptoms on the SF-MPQ in Mexican-Americans diagnosed with T2DM. This reduction in neuropathic pain symptoms was significantly correlated with increased plasma DHA levels for all participants with neuropathic pain symptoms. Reduction in neuropathic pain symptoms was not associated with significant changes in such clinical values as BMI, LDL, HDL, total cholesterol, triglycerides, HbA1c, or fasting blood glucose. Untargeted metabolomic and RF analysis showed that sphingosine levels in participants with the highest SF-MPQ sensory scores pre-supplementation were significantly elevated. Following omega-3 supplementation, sphingosine levels were markedly reduced and approached those of no-pain participants. Lastly, the reduction of pro-inflammatory and oxidative stress pathways following dietary omega-3 PUFA supplementation is consistent with the promising role of these fatty acids in reducing adverse symptoms associated with neuroinflammatory diseases and painful neuropathy.

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