HHS Public Access

Author manuscript

J Clin Psychiatry. Author manuscript; available in PMC 2017 March 28.

Published in final edited form as:

J Clin Psychiatry. 2016 February ; 77(2): e138–e143. doi:10.4088/JCP.14m09660.

Baseline Blood Levels of Omega-3 and Depression Remission: A secondary analysis of data from a placebo-controlled trial of omega-3 supplements

Robert M. Carney, Ph.D.[1], **Brian C. Steinmeyer, M.S.**[1], **Kenneth E. Freedland, Ph.D.**[1], **Eugene H. Rubin, M.D., Ph.D.**[1], **Michael W. Rich, M.D.**[2], and **William S. Harris, Ph.D.**[3]

[1]Departments of Psychiatry Washington University School of Medicine, Saint Louis, MO

[2]Medicine, Washington University School of Medicine, Saint Louis, MOCardiovascular Health Research Center, Sanford Research, University of

[3]South Dakota, Sioux Falls, SD

Abstract

Objective—Depression is associated with low red blood cell (RBC) levels of two omega-3 fatty acids (FAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), suggesting that omega-3 supplements might improve depression. However, clinical trials have produced mixed results. The purpose of this secondary analysis of data from a randomized controlled trial was to determine whether baseline blood levels of omega-3, which are known to vary widely among individuals, predict depression outcomes.

Methods—The percentages of EPA, DHA, and the omega-6 arachidonic acid (AA) were measured in RBCs at baseline and post-treatment in 122 participants with DSM-IV major depression who were randomized between May 2005 and December 2008 to receive either 50 mg/day of sertraline and 930 mg EPA/750 mg DHA/day or sertraline plus placebo. Associations between baseline RBC omega-3 levels and remission of depression (HAM-D≤7) were analyzed by treatment arm.

Results—Among participants in the omega-3 arm, baseline RBC levels of EPA+DHA (p=0.002) and the EPA+DHA:AA ratio (p=0.003) were significantly higher among those whose depression subsequently remitted compared with those whose depression did not remit. No associations were detected in the sertraline plus placebo arm. Baseline levels of EPA (p=0.03) and the EPA +DHA:AA ratio (p=0.04) moderated the relationship between treatment arm and depression outcomes.

Conclusion—High pre-treatment RBC levels of EPA and DHA, and a high EPA+DHA:AA ratio, predict favorable depression outcomes in patients receiving omega-3 supplements. Omega-3

Correspondence: Robert M. Carney, Ph.D., Behavioral Medicine Center, Washington University School of Medicine, 4320 Forest Park Avenue, Suite 301, St. Louis, MO 63108 USA; Telephone: 314-286-1313. Fax: 314-286-1301. carneyr@bmc.wustl.edu.

Financial Disclosures: Dr. Carney or a member of his family owns stock in Pfizer, Inc. Dr. Harris is the President of OmegaQuant Analytics, LLC and a Senior Research Scientist at Health Diagnostic Laboratory, Inc., and a consultant for Omthera Pharmaceuticals, Aker Biomarine Antarctica, and Tersus Pharmaceuticals. The remaining authors report no potential conflicts of interest.

Trial Registration: ClinicalTrials.gov,www.clinicaltrials.gov, NCT00116857

supplementation may be an effective treatment for depression, but the requisite dosage and duration of treatment may depend on the patient's baseline level of omega-3.

Keywords

depression; omega-3; clinical trial

Introduction

Depression is associated with low dietary intake and low plasma phospholipid and erythrocyte levels of two essential omega-3 fatty acids (FAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), in patients with[1-4] and without[5-11] coronary heart disease (CHD). As a result, there has been considerable interest in determining whether omega-3 supplements could be used to treat depression. Most of the placebo-controlled clinical trials that have investigated this question have tested either omega-3 supplements as monotherapy oromega-3 augmentation of antidepressants. The results of these trials have been mixed, and have been the subject of numerous qualitative and quantitative reviews.[12-21] Because of the heterogeneity of the trial results, these reviews have attempted to identify patient characteristics, methods of administration, and the types and dosages of omega-3 that predict treatment outcomes. Several conclusions can be drawn from this literature.

First, omega-3 augmentation of antidepressants appears to be a more promising approach than omega-3 monotherapy for depression.[13] Second, omega-3 seems to be more efficacious for major depressive disorder (MDD) than it is for subclinical depression symptoms.[13;18;19] Third, trials that have tested only or mostly EPA tended to show positive results, whereas those that have tested only or mostly DHA donot.[18;21-23] Trials of omega-3 supplements that include >60% EPA have yielded a mean depression treatment effect size (*d*) of 0.53, whereas those with <60% EPA relative to DHA have produced a mean effect size of -0.03.[21]

The optimal dosages and blood levels of EPA and DHA for treatment of depression have received little direct study. However, in a retrospective analysis of multiple clinical trials, Sublette and colleagues[21] found a nonlinear relationship in the form of a U-shaped quadratic function between depression improvement and the dosage of EPA in excess of DHA within the range of 200 to 2,200 mg/day of EPA. The blood levels of EPA and DHA that are associated with improvement in depression symptoms remain unclear.

In most pharmaceutical trials, the baseline (pre-randomization) blood level of the active drug is almost always zero. In contrast, pre-treatment blood levels of omega-3 vary considerably due to individual differences in dietary intake, the rate of incorporation into blood and tissues, and genetic variation in omega-3 fatty acid metabolism.[24] Thus, whether the necessary therapeutic level of omega-3 is actually achieved during a trial may depend not only on the dosage of omega-3 and the duration of the trial, but also on the participants' pre-treatment levels of omega-3. Higher baseline blood levels of omega-3 may make it easier to reach a therapeutic level within the time constraints of a placebo-controlled, randomized depression treatment trial. Furthermore, a higher baseline level would allow the therapeutic blood level to be achieved at a lower dose, thereby minimizing side effects and treatment

dropouts.[25] Thus, pre-randomization differences in omega-3 blood levels may explain some of the differences in the outcomes of previous trials.

The physiological pathways through which omega-3 fatty acids improve depression are unclear, but it is known that during their metabolism they help to reduce inflammatory activity which may lead, in turn, to improvement in depression symptoms.[18;21;26] For example, studies have shown that DHA and EPA suppress the production of the pro-inflammatory cytokines Il-1B, Il-6, and TNFα by monocytes and endothelial cells.[27-29] EPA inhibits the synthesis of an omega-6 fatty acid, arachidonic acid (AA), from linoleic acid, and competes with AA for its enzymatic conversion to pro-inflammatory molecules.[30;31] Omega-3 may therefore reduce depression symptoms by favorably shifting the systemic inflammatory balance towards lower inflammation. Thus, the EPA+DHA: AA ratio may also affect depression outcomes, and these ratios may also vary considerably among trial participants at baseline.

The purpose of this study was to examine the relationship between depression outcomes and baseline red blood cell (RBC) levels of DHA, EPA, and the EPA+DHA: AA ratio in depressed patients with CHD who were administered omega-3 supplements in a clinical trial.[32]

Methods

The data for this study came from a randomized, double-blinded, placebo-controlled trial to determine the efficacy of 50 mg/day of sertraline plus two capsules containing a total of 930 mg of EPA and 750 mg of DHA omega-3(Lovaza), compared to sertraline plus corn oil placebo capsules.[32] The dosage of omega-3 was based on Peet and Horrobin's[25] finding that 1 g/day of EPA produced more improvement in depression than did higher doses. EPA constituted 55% of the omega-3 supplement, just under the 60% level reported by Sublette and colleagues[21] to be associated with optimal improvement in depression.

Patients were recruited between May 2005 and December 2008 from cardiology practices and services affiliated with Washington University School of Medicine in St. Louis. The medical inclusion criteria were documented CHD defined as ≥50% stenosis in ≥1 major coronary artery, a history of revascularization, or hospitalization for an acute coronary syndrome (ACS). The exclusion criteria were cognitive impairment; psychosis or other severe psychiatric comorbidities; high risk of suicide; current substance abuse; ACS within the previous two months; left ventricular ejection fraction<30%; advanced malignancy; physical inability to participate; current use of an antidepressant, anticonvulsant, lithium, or omega-3 supplement; known sensitivity to sertraline or omega-3; and physician or patient refusal. Consenting patients who met the DSM-IV criteria for a current major depressive episode and scored ≥16 on the BDI-II[33] were enrolled in the study. A blood sample was obtained and the 17-item Hamilton Rating Scale (HAM-D-17) was administered at baseline and after ten weeks of treatment to assess treatment outcomes.[34] The study was approved by the Human Research Protection Office at Washington University, and all participants signed an approved informed consent form.

Unused medications were counted and subtracted from the number provided to determine adherence. Measures of total red blood cell membrane EPA, DHA, and AA were obtained at baseline and post-treatment assessments and assayed by capillary gas chromatography after extraction and conversion to fatty acid methyl esters.[35] Red blood cell levels of each fatty acid were expressed as the percentage of the total fatty acids. Dietary intake of fish containing high levels of omega-3 FAs was estimated before and during the trial using a brief structured dietary recall interview that asked participants to report the number of servings (3.5 oz.) of any of 30 fatty fishes that are known to be high in EPA and DHA.

Statistical Analysis: Chi-square tests and analysis of variance (ANOVA) models were used to compare pre-specified baseline fatty acids and other clinical, medical, and demographic variables between patients whose depression subsequently remitted (HAM-D-17≤ 7)and those who did not achieve remission. Analysis of covariance (ANCOVA) was used to determine whether baseline RBC levels of EPA, DHA, or the EPA+DHA: AA ratio moderated the relationship between treatment assignment and depression outcomes. Post-treatment HAM-D-17 scores were regressed on the percentage of the fatty acid in red blood cells, a dichotomous indicator for treatment arm assignment, the HAM-D-17 score at baseline, and the interaction between treatment assignment and the percent of the fatty acid in RBCs. A similar analysis was conducted with the number of fatty fish portions reportedly consumed in the previous month.

Distributional assumptions were verified and residual analyses were performed on each statistical model. All statistical tests were 2-sided with a Type I error rate set at the 0.05 level. All analyses were performed using SAS statistical software, version 9.3.

Results

As previously reported, there were no differences between the sertraline plus placebo [P] (n=60) and sertraline plus omega-3 [O] (n=62)arms in pre-post HAM-D-17change scores (9.4 [P] vs. 9.3 [O]; p = 0.90) or in pre-post BDI-II change scores (14.8 [P] vs. 16.1 [O]; p = 0.44).[32] Furthermore, the groups did not differ after treatment on depression remission (HAM-D-17 <7). Remission occurred in 27 (46.6%) of the participants in the omega-3 arm, and 27 (49.1%) of the patients in the placebo arm. The demographic and medical characteristics of the remitters and non-remitters are presented by treatment arm in Table 1. The prevalence of diabetes differed between remitters and non-remitters in the omega-3 arm. However, diabetes was unrelated to either baseline EPA/DHA levels (p=0.32), or to change in EPA/DHA levels following treatment (p=0.77). There were no differences between remitters and non-remitters on any variable in the placebo arm.

As expected, omega-3 fatty acid RBC levels rose significantly in the omega-3 group following treatment, but changed very little in the placebo arm (Table 2). Baseline RBC levels of EPA+DHA were higher in the remitted than the non-remitted participants who had received omega-3 (p=0.002), and the remitted participants tended to have higher RBC levels of EPA+DHA following treatment than did the non-remitters (p=0.07). There were no differences in RBC levels of EPA+DHA at baseline or post-treatment between remitted and non-remitted participants in the placebo arm. Adherence to the omega-3 or placebo capsule

and sertraline regimens exceeded 97% in both groups, with no significant between-group differences.

The baseline level of AA did not differ between remitters and non-remitters in either arm, but the ratio of EPA+DHA:AA was significantly higher among the remitters than the nonremitters in the omega-3 arm (p=0.003). There was also a trend toward a difference in the EPA+DHA:AA ratio between remitters and non-remitters following treatment in the omega-3 arm (p=0.09). In contrast, there were no differences in any of these between remitters and non-remitters in the placebo arm. Consistent with the baseline RBC levels of omega-3, the self-reported number of fatty fish servings consumed in the month prior to study enrollment was higher in the remitters than in the non-remitters in the omega-3 arm, and tended to be higher in those who remitted in the placebo arm (p=0.07). The correlation between self-reported consumption of fatty fish and baseline levels of EPA+DHA was 0.28 (p=0.002).

ANCOVAs were conducted to determine whether baseline RBC levels of EPA, DHA, EPA +DHA:AA, or the consumption of fatty fish in the prior month, moderated the relationship between treatment arm and depression outcome. The interactions between treatment arm and baseline RBC level of EPA (p=0.03) and the baseline EPA+DHA:AA ratio (p=0.04) were significant. Both therefore moderated the relationship between treatment arm and depression outcomes. There was also a trend toward an interaction between treatment arm and pre-treatment EPA+DHA (p=0.08) and DHA alone (p=0.07). The interaction between treatment assignment and the number of fatty fish portions consumed in the prior month to baseline was not significant (p=0.17).

There was a significant linear relationship between baseline and post-treatment omega-3 (EPA+DHA) blood levels ($r = 0.71$; $p<0.0001$) in the omega-3 arm. Predicted probabilities from a logistic regression model (probability of remission regressed on omega-3 blood levels and baseline HAM-D-17 score) was used to classify patients as having either a “high” (≥ 60%) or a “low” (<60%) probability of remission, and to compare the distribution of baseline and post-treatment omega-3 blood levels between these two groups (Table 3). In general, the higher the baseline EPA+DHA level the higher the post-treatment EPA+DHA level and the greater the probability of remission.

Discussion

We previously reported the primary results of this double-blind, randomized, placebo-controlled trial of omega-3 augmentation of sertraline.[32] Although we found that this combination of EPA and DHA had some cardiovascular benefits[36], it was not efficacious for depression.[32] As hypothesized for this secondary analysis, baseline RBC levels of EPA, DHA, the EPA+DHA:AA ratio, as well as the reported number of servings of fatty fish rich in omega-3 consumed in the month prior to enrollment in the clinical trial, were significantly higher among patients in the omega-3 arm whose depression subsequently remitted than in those whose depression did not remit. In addition, we found that the percentage of EPA in RBCs at baseline and the EPA+DHA:AA ratio moderated the relationship between treatment group and depression outcomes. There was also a trend for baseline RBC levels of DHA to

moderate improvement in depression. These results suggest that if all participants in the trial had begun with higher RBC levels of omega-3, especially EPA, there might have been a significant between-group, post-treatment difference in depression.

Omega-3 and omega-6 are essential fatty acids that must be obtained through dietary intake. While the blood level of a study drug can ordinarily be assumed to be zero before a trial begins, this assumption is not warranted in trials of food supplements such as omega-3 fatty acids. Higher baseline blood levels of omega-3 may make it easier to reach a therapeutic level within the normal duration of a placebo-controlled, depression trial.

High baseline levels of EPA and DHA may result from a diet high in these omega-3 fatty acids. It is also possible that participants with higheromega-3 levels at baseline incorporate these fatty acids into RBCs and other tissues more efficiently than do those with lower levels of omega-3, and are therefore better able to utilize the omega-3provided by the supplements. There are large individual differences in the plasma and RBC uptake of omega-3, even with an identical diet. In both short-and long-term studies, a fixed daily dose of omega-3 produces substantial individual variability in omega-3 blood levels[37], which may be explained in part by genetic polymorphisms.[38] Lower blood and tissue uptake of omega-3 may help to explain the lower levels of EPA and DHA found in depressed patients, and may even have etiological significance.

However, the number of servings of fish rich in omega-3 consumed during the month before enrollment in the trial was also higher in the remitters compared to the nonremitters in the group receiving the omega-3 supplement. It tended to be higher in the remitters compared to non-remitters in the sertraline plus placebo arm, but it did not moderate the effect of treatment assignment on depression outcomes. The correlation between the estimated number of fish servings and omega-3 blood levels was only moderate (r=0.28), accounting for less than 10% of the variance in omega-3 levels. In addition to the wide variability in the uptake of omega-3 from food or supplements, this low correlation may be due to the difficulty in obtaining accurate and reliable estimates of diet using standard self-report or interview-based dietary assessments.[39] It is important to acknowledge, however, that the dietary interview used in this study only considered a list of fish known to be high in DHA and EPA, and when adding fish servings (approximately 3.5 ounces) it did not distinguish between type of fish (e.g. tuna vs. salmon) although DHA+EPA levels in these fish vary considerably.

The optimal therapeutic blood (RBC or plasma) levels of omega-3 associated with successful omega-3 treatment of major depression, either alone or in combination with antidepressants, has received little study. However, studies have compared plasma or RBC levels of EPA+DHA between patients with major depression and healthy controls.[40] Although plasma and RBC omega-3 levels correlate, RBC levels are less sensitive to recent intake of omega-3, and therefore tend to provide more reliable, stable estimates of omega-3 levels over time.[41;42] In three studies comparing EPA+DHA in RBCs in individuals with major depression and healthy controls, the mean percentages of RBC of omega-3 in depressed patients were 3.6, 3.6, and 3.8, vs. 6.3, 5.4, and 4.8 in the non-depressed participants.[6;10;11] These findings suggest that a level of 5-6% in RBCs might be a

reasonable target for therapeutic efficacy. However, patients whose depression did not remit in the present study nevertheless increased their omega-3 RBC levels to an average of 7.2%, compared to 8% for the remitters. Further analysis of these data revealed that the probability of remission was highest in the participants in the omega-3 arm who had the highest blood levels after treatment, in the range of 9-10%, and these participants also had the highest blood levels before the trial began. This finding is similar to that reported in a review of trials of omega-3 to improve cardiovascular outcomes which concluded that the beneficial effects of omega-3 on cardiovascular outcomes in clinical trials were achieved by the patients who reached the highest blood levels of omega-3, which in many cases were higher than those typically observed in healthy controls.[38]

The levels associated with depression reported in the studies of otherwise medically-well participants[6;10;11] are similar to those found inpatients with CHD.[38;43;44] Numerous clinical trials have investigated the effects of omega-3 on cardiovascular outcomes. These studies were recently reviewed by Superko and his colleagues.[38] They found wide variability in blood levels of omega-3 in clinical trial participants who received identical dosages of omega-3.They concluded that because of individual variability in blood levels following treatment, blood levels of omega-3 may be better markers of CVD risk/benefit than simple assignment to a fixed dose of omega-3 supplementation. Further more, they noted that including subjects who achieved less than therapeutic blood levels may have diluted the beneficial effect of omega-3 on CVD endpoints. These observations may also apply to depression clinical trials.

It is important to note that participants in this study had major depressive disorder and CHD. Cardiovascular disease and other comorbid medical diseases present in these patients may affect omega-3 metabolism and utilization, and the relationship of RBC levels to depression outcomes. Thus, the generalizability of these findings to medically well psychiatric patients is not clear. It is also important to note that the present data were collected for a randomized clinical trial. The trial was not designed to determine therapeutic levels of omega-3 that night be needed to improve depression outcomes. Studies designed to determine the range of omega-3 blood levels and the duration of exposure to these levels that are required to maximize the probability of remission are needed. In addition, more work is needed to identify the genetic, metabolic, medical, and dietary factors that may moderate the dose/response relationship between omega-3 and depression improvement, similar to the research that has been reported concerning the dosing requirements for vitamin D supplementation.[45]

Acknowledgments

Sources of Financial Support: This study was supported in part by Grants R01 HL076808 and R01 HL117805 from the National Heart, Lung, and Blood Institute (Robert M. Carney.PI).Glaxo-Smith-Kline, Inc. (formally Reliant) provided Lovaza (omega-3) and placebo capsules, andPfizer, Inc. provided Zoloft (sertraline) for this study. The investigators had sole control over the design, planning, execution, and reporting of the results of this study.

References

1. Ali S, Garg SK, Cohen BE, et al. Association between omega-3 fatty acids and depressive symptoms among patients with established coronary artery disease: data from the Heart and Soul Study. Psychother Psychosom. 2009; 78(2):125–127. [PubMed: 19223688]

2. Amin AA, Menon RA, Reid KJ, et al. Acute coronary syndrome patients with depression have low blood cell membrane omega-3 fatty acid levels. Psychosom Med. 2008; 70(8):856–862. [PubMed: 18842751]

3. Frasure-Smith N, Lesperance F, Julien P. Major depression is associated with lower omega-3 fatty acid levels in patients with recent acute coronary syndromes. Biol Psychiatry. 2004; 55(9):891–896. [PubMed: 15110732]

4. Parker GB, Heruc GA, Hilton TM, et al. Low levels of docosahexaenoic acid identified in acute coronary syndrome patients with depression. Psychiatry Res. 2006; 141(3):279–286. [PubMed: 16499974]

5. Baghai TC, Varallo-Bedarida G, Born C, et al. Major depressive disorder is associated with cardiovascular risk factors and low Omega-3 Index. J Clin Psychiatry. 2011; 72(9):1242–1247. [PubMed: 21208589]

6. Edwards R, Peet M, Shay J, et al. Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients. J Affect Disord. 1998; 48(2-3):149–155. [PubMed: 9543204]

7. Hibbeln JR. Fish consumption and major depression. Lancet. 1998; 351(9110):1213.

8. Kiecolt-Glaser JK, Belury MA, Porter K, et al. Depressive symptoms, omega-6:omega-3 fatty acids, and inflammation in older adults. Psychosom Med. 2007; 69(3):217–224. [PubMed: 17401057]

9. Lin PY, Huang SY, Su KP. A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. Biol Psychiatry. 2010; 68(2):140–147. [PubMed: 20452573]

10. McNamara RK, Jandacek R, Rider T, et al. Selective erythrocyte omega-3 fatty acid deficits in adult patients with bipolar disorder: comparison with major depressive disorder. Biol Psychiatry. 2009; 65:S140.

11. Peet M, Murphy B, Shay J, et al. Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. Biol Psychiatry. 1998; 43(5):315–319. [PubMed: 9513745]

12. Appleton KM, Hayward RC, Gunnell D, et al. Effects of n-3 long-chain polyunsaturated fatty acids on depressed mood: systematic review of published trials. Am J Clin Nutr. 2006; 84(6):1308–1316. [PubMed: 17158410]

13. Appleton KM, Rogers PJ, Ness AR. Updated systematic review and meta-analysis of the effects of n-3 long-chain polyunsaturated fatty acids on depressed mood. Am J Clin Nutr. 2010; 91(3):757–770. [PubMed: 20130098]

14. Freeman MP, Hibbeln JR, Wisner KL, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. J Clin Psychiatry. 2006; 67(12):1954–1967. [PubMed: 17194275]

15. Grosso G, Pajak A, Marventano S, et al. Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. PLoS One. 2014; 9(5):e96905. [PubMed: 24805797]

16. Lin PY, Su KP. A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. J Clin Psychiatry. 2007; 68(7):1056–1061. [PubMed: 17685742]

17. Logan AC. Neurobehavioral aspects of omega-3 fatty acids: possible mechanisms and therapeutic value in major depression. Altern Med Rev. 2003; 8(4):410–425. [PubMed: 14653768]

18. Martins JG. EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. J Am Coll Nutr. 2009; 28(5):525–542. [PubMed: 20439549]

19. Sarris J, Schoendorfer N, Kavanagh DJ. Major depressive disorder and nutritional medicine: a review of monotherapies and adjuvant treatments. Nutr Rev. 2009; 67(3):125–131. [PubMed: 19239627]

20. Sontrop J, Campbell MK. Omega-3 polyunsaturated fatty acids and depression: a review of the evidence and a methodological critique. Prev Med. 2006; 42(1):4–13. [PubMed: 16337677]

21. Sublette ME, Ellis SP, Geant AL, et al. Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression. J Clin Psychiatry. 2011; 72(12):1577–1584. [PubMed: 21939614]

22. Martins JG, Bentsen H, Puri BK. Eicosapentaenoic acid appears to be the key omega-3 fatty acid component associated with efficacy in major depressive disorder: a critique of Bloch and Hannestad and updated meta-analysis. Mol Psychiatry. 2012; 17(12):1144–1149. [PubMed: 22488258]

23. Bloch MH, Hannestad J. Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis. Mol Psychiatry. 2012; 17(12):1272–1282. [PubMed: 21931319]
24. Simopoulos AP. Genetic variants in the metabolism of omega-6 and omega-3 fatty acids: their role in the determination of nutritional requirements and chronic disease risk. Exp Biol Med (Maywood). 2010; 235(7):785–795. [PubMed: 20558833]
25. Peet M, Horrobin DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. Arch Gen Psychiatry. 2002; 59(10):913–919. [PubMed: 12365878]
26. Muskiet FA, Fokkema MR, Schaafsma A, et al. Is docosahexaenoic acid (DHA) essential? Lessons from DHA status regulation, our ancient diet, epidemiology and randomized controlled trials. J Nutr. 2004; 134(1):183–186. [PubMed: 14704315]
27. Chu AJ, Walton MA, Prasad JK, et al. Blockade by polyunsaturated n-3 fatty acids of endotoxin-induced monocytic tissue factor activation is mediated by the depressed receptor expression in THP-1 cells. J Surg Res. 1999; 87(2):217–224. [PubMed: 10600352]
28. Khalfoun B, Thibault F, Watier H, et al. Docosahexaenoic and eicosapentaenoic acids inhibit in vitro human endothelial cell production of interleukin-6. Adv Exp Med Biol. 1997; 400B:589–597. [PubMed: 9547608]
29. Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nat Rev Immunol. 2008; 8(5):349–361. [PubMed: 18437155]
30. Anderson BM, Ma DW. Are all n-3 polyunsaturated fatty acids created equal? Lipids Health Dis. 2009; 8:33. [PubMed: 19664246]
31. Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. J Am Coll Nutr. 2002; 21(6):495–505. [PubMed: 12480795]
32. Carney RM, Freedland KE, Rubin EH, et al. Omega-3 augmentation of sertraline in treatment of depression in patients with coronary heart disease: a randomized controlled trial. JAMA. 2009; 302(15):1651–1657. [PubMed: 19843899]
33. Beck, AT., Steer, RA., Brown, GK. Manual for the BDI-II. San Antonio, TX: Psychological Corporation; 1996.
34. Freedland KE, Skala JA, Carney RM, et al. The Depression Interview and Structured Hamilton (DISH): rationale, development, characteristics, and clinical validity. Psychosom Med. 2002; 64(6):897–905. [PubMed: 12461195]
35. Harris WS, von Schacky C. The Omega-3 Index: a new risk factor for death from coronary heart disease? Prev Med. 2004; 39(1):212–220. [PubMed: 15208005]
36. Carney RM, Freedland KE, Stein PK, et al. Effect of omega-3 fatty acids on heart rate variability in depressed patients with coronary heart disease. Psychosom Med. 2010; 72(8):748–754. [PubMed: 20716712]
37. Flock MR, Skulas-Ray AC, Harris WS, et al. Determinants of erythrocyte omega-3 fatty acid content in response to fish oil supplementation: a dose-response randomized controlled trial. J Am Heart Assoc. 2013; 2(6):e000513. [PubMed: 24252845]
38. Superko HR, Superko SM, Nasir K, et al. Omega-3 fatty acid blood levels: clinical significance and controversy. Circulation. 2013; 128(19):2154–2161. [PubMed: 24190935]
39. Joachim G. Sources of variability in the reproducibility of food frequency questionnaires. Nutr Health. 1998; 12(3):181–188. [PubMed: 9670173]
40. McNamara RK. Membrane omega-3 Fatty Acid deficiency as a preventable risk factor for comorbid coronary heart disease in major depressive disorder. Cardiovasc Psychiatry Neurol. 2009; 2009:362795. [PubMed: 19936106]
41. Harris WS, Thomas RM. Biological variability of blood omega-3 biomarkers. Clin Biochem. 2010; 43(3):338–340. [PubMed: 19733159]
42. Harris WS, Varvel SA, Pottala JV, et al. Comparative effects of an acute dose of fish oil on omega-3 fatty acid levels in red blood cells versus plasma: implications for clinical utility. J Clin Lipidol. 2013; 7(5):433–440. [PubMed: 24079284]
43. Block RC, Harris WS, Reid KJ, et al. EPA and DHA in blood cell membranes from acute coronary syndrome patients and controls. Atherosclerosis. 2008; 197(2):821–828. [PubMed: 17875307]

44. Pottala JV, Garg S, Cohen BE, et al. Blood eicosapentaenoic and docosahexaenoic acids predict all-cause mortality in patients with stable coronary heart disease: the Heart and Soul study. Circ Cardiovasc Qual Outcomes. 2010; 3(4):406–412. [PubMed: 20551373]

45. Singh G, Bonham AJ. A predictive equation to guide vitamin d replacement dose in patients. J Am Board Fam Med. 2014; 27(4):495–509. [PubMed: 25002004]

Clinical Points

- Studies evaluating the efficacy of omega-3 supplements for depression have produced mixed results. As blood levels of these essential fatty acids may vary from person to person before beginning treatment, this study asked whether initial blood levels predict final depression outcomes.
- The study found that initial blood levels of omega-3 fatty acids do predict response to treatment. Baseline levels of omega-3 may need to be considered when determining omega-3 dose and the duration of treatment to maximize effectiveness.

Table 1

Demographic and medical characteristics by post- treatment remission status (HAM-D-17 <7)

INTERVENTION GROUP	Remission (HAM-D-17 ≤ 7)		P
	No (n = 31)	Yes (n = 27)	
Demographics			
Gender (% Female)	9 (29.0)	10 (37.0)	.52
Age (in years)	58.0 ± 10.2	59.0 ± 7.9	.69
Caucasian	22 (71.0)	24 (88.9)	.09
Medical			
Current cigarette smoker	11 (35.5)	5 (18.5)	.15
Body mass index (kg/m^2)	33.2 ± 7.0	34.8 ± 8.0	.41
Diabetes mellitus	14 (45.2)	4 (14.8)	.01
History revascularization	24 (77.4)	23(85.2)	.45
History of hypertension	24 (77.4)	20 (74.1)	.77
Creatinine (mg/dl)	0.95 ± 0.24	0.93 ± 0.28	.76
Medications and Biomarkers			
Beta blocker	24 (77.4)	21 (77.8)	.97
ACE inhibitor	18 (58.2)	11 (40.7)	.19
Aspirin	23 (74.2)	19 (70.4)	.75
Statins	19 (61.3)	22 (81.5)	.09
Insulin	6 (19.4)	2 (7.4)	.26

PLACEBO GROUP	Remission (HAM-D-17 ≤ 7)		P
	No (n = 28)	Yes (n = 27)	
Demographics			
Gender (% Female)	9 (32.1)	8 (29.6)	.84
Age (in years)	57.9 ± 9.8	58.9 ± 7.6	.69
Caucasian	23 (82.1)	22 (81.5)	.95
Medical			
Current cigarette smoker	7 (25.0)	4 (14.8)	.35
Body mass index (kg/m^2)	32.1 ± 6.0	33.4 ± 8.5	.53
Diabetes mellitus	11 (39.3)	13 (48.2)	.51
History revascularization	24 (85.7)	24 (88.9)	.72
History of hypertension	23 (82.1)	22 (81.5)	.95
Creatinine (mg/dl)	0.97 ± 0.32	0.92 ± 0.23	.48
Medications			
Beta blocker	24 (85.7)	21 (77.8)	.45
ACE inhibitor	13 (46.4)	12 (44.4)	.88
Aspirin	23 (82.1)	26 (96.3)	.09

PLACEBO GROUP	Remission (HAM-D-17 ≤ 7)		P
	No (n = 28)	Yes (n = 27)	
Statins	21 (75.0)	21 (77.8)	.81
Insulin	8 (28.6)	3 (11.1)	.11

Continuous variables are reported as (mean ± SD); categorical variables represent number of patients (%)

Table 2

Omega-3 and Omega-6 FA red blood cell (RBC) levels and adherence by post-treatment remission status

INTERVENTION GROUP	Remission (HAM-D ≤ 7)		
Fatty Acid (% in RBC)	**No (n = 31)**	**Yes (n = 27)**	**P**
EPA+DHA			
Baseline	4.1 ± 0.9	5.3 ± 1.9	.002
Post-treatment	7.2 ± 1.5	8.0 ± 2.0	.07
EPA			
Baseline	.47 ± .11	.61 ± .31	.02
Post-treatment	1.5 ± .6	1.6 ± .7	.51
DHA			
Baseline	3.7 ± 1.0	4.7 ± 1.7	.004
Post-treatment	5.7 ± 1.1	6.4 ± 1.5	.048
Arachidonic acid (AA)(omega-6)			
Baseline	18.4 ± 1.7	17.8 ± 2.2	.31
Post-treatment	16.5 ± 3.1	16.0 ± 2.5	.48
EPA+DHA:AA ratio			
Baseline	.23 ± .06	.30 ± .12	.003
Post-treatment	.45 ± .12	.52 ± .16	.09
Omega-3/Placebo Compliance (%)	97.6 ± 3.1	97.3 ± 5.5	.78
Sertraline Compliance (%)	99.0 ± 2.3	98.2 ± 3.9	.35
Fish intake (mean servings/week)	0.3 ± 0.3	1.0 ± 1.5	.02
Number of reported side effects	0.6 ± 1.8	0.8 ± 2.2	.62

PLACEBO GROUP	Remission (HAM-D ≤ 7)		
Fatty Acid (% in red blood cells [RBC])	**No (n = 28)**	**Yes (n = 27)**	**P**
EPA+DHA			
Baseline	4.7 ± 1.5	4.6 ± 1.3	.75
Post-treatment	4.6 ± 1.3	4.5 ± 1.0	.74
EPA			
Baseline	.60 ± .22	.49 ± .23	.10
Post-treatment	.56 ± .23	.45 ± .26	.18
DHA			
Baseline	4.2 ± 1.4	4.1 ± 1.1	.75
Post-treatment	4.1 ± 1.1	4.0 ± 1.0	.77
Arachidonic acid (AA)			
Baseline	17.7 ± 2.5	17.7 ± 2.1	.99
Post-treatment	17.7 ± 1.8	17.7 ± 2.3	.94

PLACEBO GROUP	Remission (HAM-D ≤ 7)		
Fatty Acid (% in red blood cells [RBC])	**No (n = 28)**	**Yes (n = 27)**	**P**
EPA+DHA:AA ratio			
Baseline	.28 ± .12	.27 ± .10	.67
Post-treatment	.27 ± .09	.26 ± .09	.72
Omega-3/Placebo Compliance (%)	98.1 ± 2.4	97.1 ± 3.0	.20
Sertraline Compliance (%)	98.5 ± 3.2	98.7 ± 1.9	.86
Fish intake (mean servings/week)	0.5 ± 0.6	0.9 ± 1.2	.07
Number of reported side effects	1.4 ± 3.3	0.5 ± 1.0	.21

Continuous variables are reported as (mean ± SD); categorical variables represent number of patients (%) Abbreviations: RBC, red blood cell; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; AA, arachidonic acid.

Table 3

Logistic regression model predicting probability of remission based on baseline and post treatment levels of EPA+DHA

EPA+DHA Levels	Predicted probability of remission	
	LOW (<60%) (n=44)	HIGH (≥60%) (n=18)
Baseline EPA+DHA (%)		
Mean ± SD	3.9 ± 0.8	6.3 ± 1.6
25th percentile	3.3	5.2
Median	3.9	6.0
75th percentile	4.6	7.3
(min, max)	(2.4, 5.5)	(4.1, 9.7)
Post Treatment EPA+DHA (%)		
Mean ± SD	7.1 ± 1.4	8.7 ± 2.0
25th percentile	6.3	7.7
Median	7.1	8.2
75th percentile	8.3	9.1
(min, max)	(3.8, 9.9)	(5.5, 14.1)

Abbreviations: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.