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Research Article

# An Up-to-date Marker of Heart Health - The Omega-3 Index!

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## Abstract

Circulating levels of omega-3 PUFA and their erythrocyte membrane levels (omega-3 index) inversely associate with cardiovascular events. As flaxseed oil and fish oil have complementary cardioprotective benefits, the combined effect of a daily supplementation of ALA (868.98 mg), EPA (358.2 mg) and DHA (238.4 mg) was studied in pre-obese, mild hypercholesterolemic women using a pre-test, post-test research design. 30 premenopausal and 30 postmenopausal subjects (equally assigned to control and test groups) underwent two week baseline, 60 days study/supplementation and two week withdrawal (test group alone) periods. The combined supplementation was significantly hypocholesterolemic, hypotensive, anti-inflammatory and obesity-lowering alongside improving omega-3 index.

**Keywords**: PUFA (Polyunsaturated Fatty Acids); ALA (Alpha-linolenic Acid); EPA (Eicosapentaenoic Acid); DHA (Docosahexaenoic Acid); Mild Hypercholesterolemia (Total Cholesterol-200 to 239 mg/dL); Omega-3 Index (Sum of EPA and DHA in the Erythrocyte Membrane, Expressed in Percentage); LDL-C (Low Density Lipoprotein Cholesterol); VLDL-C (Very Low Density Lipoprotein Cholesterol); HDL-C (High Density Lipoprotein Cholesterol)

## Introduction

In the modern diet, omega-6 fatty acids have predominantly gained importance, and consequently raised the omega-6 to omega-3 fatty acid ratio many-fold than the optimal value. This ratio distraction away from the optimum paves way for cardiovascular disturbances by aggravating dyslipidemia, vasoconstriction, inflammation, and platelet aggregation. As against a ratio of 4:1 (omega-6:omega-3), the recent years are witnessing an approximate ratio of 20:1, which is very much in favor of omega-6. Hence, there is a need to advocate the intake of heart-healthy omega-3 fatty acids in recommended amounts to counter-balance the effects of excessive omega-6 fatty acid intake [1].

A recent meta-analysis by Benasconi and colleagues [2] considered 42 studies (including the STRENGTH and OMEMI trials) covering a total of 149,359 participants. The cardio-protective benefits of omega-3 fatty acids were quantitatively established as statistically significant reductions in fatal myocardial infarction (35%), all myocardial infarctions (13%), and coronary heart disease mortality (9%). Thus regular and adequate intake of omega-3 fatty acids is an effective lifestyle intervention for protection against cardiovascular diseases [3].

At estimated biologically equivalent intakes, the plant and marine sources of omega-3 fatty acids namely ALA and EPA, DHA have different cardioprotective benefits [4-7]. Alpha-linolenic

acid from flaxseed oil influences concentrations of serum total cholesterol, LDL-C and apo lipoprotein B more favorably than EPA plus DHA [8]. Whereas EPA and DHA from fish oil effectively reduce serum triglycerides, VLDL-C levels and increase HDL-C levels more significantly compared to ALA. Physiologically EPA produces a series of eicosanoids which enhance nitric oxide production, and, prevent vasoconstriction, inflammation, platelet aggregation, and arrhythmias.

Health saviors such as omega-3 fatty acids are univocally recommended owing to cardiovascular disease prevention. Nevertheless their bioavailability determines their efficacy and dosage recommendation. A biomarker that reflects the bioavailability and consequent cellular happenings at a given point in time is very crucial, as it can relate with the subsequent ill-health of a vital organ. Same holds true with omega-3 index! Omega-3 index assesses the erythrocyte percentage of EPA and DHA using a standardized analytical procedure [9]. Omega-3 index negatively correlates with cardiovascular risk; an index less than 4% marks high risk, while an index of >8% relates with a low risk [10]. A global survey on omega-3 index was conducted considering the circulating EPA and DHA levels from 24,129 subjects across 54 countries through 398 datasets. These circulating levels were converted into an equivalent omega-3 index which revealed lower values (Omega-3 Index of <4%) amongst Americans, Canadians, Indians and Brazilians; moderate values (Omega-3 Index at 4% to 8%) amongst Russians, Chinese, Australians, and Western Europeans; and higher values (Omega-3 Index of >8%) amongst the Greenlanders, Norwegians, Japanese and Koreans [11].

Researches establishing the positive role of omega-3 fatty acids in heart health promotion pile up every second. Still there appears a gap in the literature with regard to their efficiency in a combined form, and the minimally required supplementation dose and duration. Evidences from recent researches including the Framingham and Helsinki study insist that cardiovascular diseases pose a major morbidity and mortality threat even in women.

Hence, in order to achieve favorable reductions in potentially atherogenic LDL-C through ALA, as well as simultaneously reduce the risk of hypertriglyceridemia, blood clot formation and eventual heart attacks through EPA and DHA, the present study focused on a combined supplementation of a daily dose of 868.98 mg of ALA, 358.2 mg of EPA and 238.4 mg of DHA (from one flaxseed oil and two fish oil capsules) in pre-obese, mild hypercholesterolemic women. Supplementation dosage was in accordance with the recommendations stated by American Dietetic Association and Dietitians of Canada [15,16].

## Materials and Methods

A case-control study with pre-test, post-test experimental design was employed with an inclusion of 60 study participants, who were free-living residents of Chennai district in Tamil Nadu, India. Informed consent was obtained from all the participants after duly explaining the research perspectives based on ethical norms. A schematic representation of the study design is presented in the following figure (Figure 1).

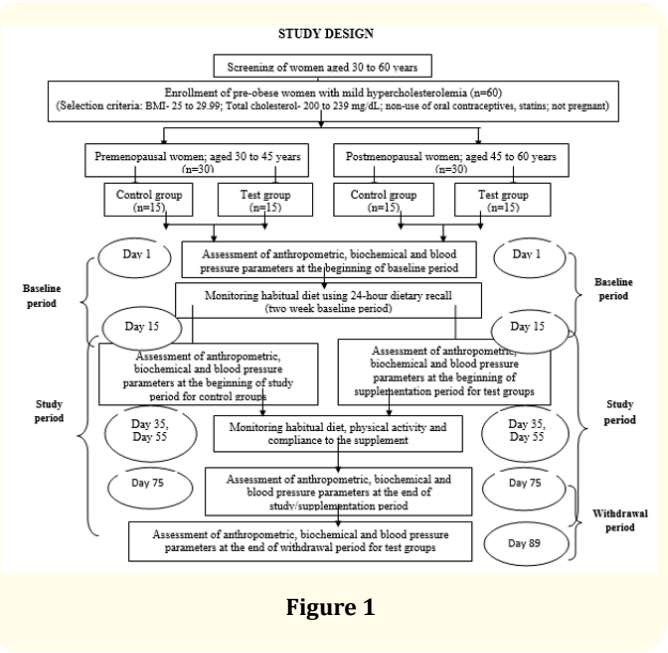


**Figure 1**

Assessment indices included anthropometric measurements (body weight, body mass index, waist circumference, hip circumference and waist: hip ratio); selected biochemical parameters (serum C-reactive protein/CRP levels, serum lipid profile, omega-3 index); clinical measures (blood pressure levels) and routine monitoring of habitual diet and physical activity. As the beneficial effects of omega-3 PUFA appear to arise primarily from their effects on cellar membranes, measuring their erythrocyte membrane concentrations (omega-3 index) is a rational approach

to biostatus assessment [13]. Hence, this recent and effective marker which inversely correlates with the risk of cardiovascular events was innovatively included in the study.

Information pertaining to Socio-demographic profile, personal habits, present illness (if any) and family history of disease conditions were collected at the beginning of the study using an interview schedule. Dietary pattern was assessed using a 3 day dietary recall and food frequency questionnaire.

Analysis of serum lipid parameters and serum CRP levels were carried out in the Lister Metropolis Laboratory, Anna Nagar, Chennai using the following estimation methods-

- Serum total cholesterol level by CHOD-PAP enzymatic endpoint method
- Serum LDL cholesterol level by the Automated Low Density lipoprotein (ALDL) method, using the beta-quantification determination of LDL-C concentration
- Serum HDL cholesterol level by the direct enzyme clearance method
- Serum triglycerides level using the GPO-PAP method
- Estimation of serum C-reactive protein by Nephelometry.

Estimation of Erythrocyte fatty acid composition was carried out using gas chromatography (with the assay employing methyl/ ethyl esters) at ATOZ laboratories, Ambatur, Chennai.

The systolic and diastolic blood pressure readings were recorded using a standard mercury sphygmomanometer (in seated position after the subject had rested for at least 10 minutes).

### Statistical analysis

Demographic, dietary, anthropometric, biochemical and baseline clinical characteristics were summarized as mean ± SD for continuous variables and as a percentage of the group for dichotomous (categorized) variables. Paired 't' test and Independent 't' test were used to assess the change in anthropometric measurements, blood pressure, serum C-reactive protein, lipid parameters and omega-3 index of all the subjects. Karl Pearson's co-efficient of correlation was performed to study the association between the different variables. P value <0.05 was considered as statistically significant. Data were statistically analyzed using SPSS software for Windows version 14.0, SPSS Inc, Chicago, USA.

## Results and Discussion

### Combined supplementation optimized dietary omega-6: omega-3 ratio by improving omega-3 levels

The mean energy intake of the subjects was 2495 to 2498 kilocalories per day. The percentage of energy derived from SFA (13%) was quite high compared to MUFA (9%) and PUFA (6%). The percentage of energy derived from ALA was only 0.3 per cent while LA provided 6 per cent of energy, hence the dietary omega-6: omega-3 ratio of 5.6: 0.3, revealed a dietary excess of LA/ omega-6 intake. Though all the subjects were non-vegetarians, their fish intake was less frequent (once in two weeks), which would also have contributed to the low omega-3 intake. In the test group, the combined supplementation increased the omega-3 levels three-fold rendering an improved ratio of 5.6:0.9. This improvement seen in the omega-6: omega-3 ratio due to the combined supplementation was statistically significant ($p < 0.01$).

### Notable findings in Anthropometric measurements

The mean BMI of the premenopausal (26.6 ± 1.4) and postmenopausal (26.3 ± 1.4) subjects in the control and test groups was in the pre-obese range. Their mean waist circumference measures (premenopausal: 93.4 ± 2.8; postmenopausal: 95.0 ± 4.0) revealed the presence of abdominal obesity based on the cut-off points set by the WHO expert consultation (≥ 88 cm in women and ≥ 102 cm in men), and this could have contributed to their unfavorable serum lipid profile. Abdominal obesity increases the risk of dyslipidemia. Abdominal fat and circulating triglycerides increase with age, which indicates lipid over accumulation. The baseline values of abdominal obesity measures were comparatively higher in the postmenopausal subjects.

Increase in BMI above the normal range may be accompanied by a modest rise in total cholesterol, a steady increase in LDL-C and a consistent decrease in HDL-C. In the present study, pre-obese subjects with abdominal obesity had baseline mean serum total cholesterol levels in the range of mild hypercholesterolemia, additionally their triglyceride and LDL-C levels were in the borderline-high range and HDL-C levels were low, based on the WHO, Pan American Health Organization (2006) [14].

Dietary omega-3 PUFA have a suppressive effect on the lipogenic enzyme, fatty acid synthase, and ALA supplementation favorably influences adinopectin levels. In accordance with the above review, a combined supplementation of flaxseed oil with fish oil providing 0.9 per cent of energy along with a habitual diet significantly reduced the BMI by 4.66 per cent and 5.29 per cent in premenopausal and postmenopausal women. The mean difference observed in the anthropometric measurements between the control and test groups in premenopausal as well as postmenopausal subjects after the study/ supplementation period was statistically significant ($p < 0.001$).

## Noteworthy results and interpretations in the assessment of serum lipid parameters and CRP levels

The Helsinki Heart Study and the Nurses' Health Study have reported that a combination of high triglyceride (> 150 mg/dl), low HDL-C (< 40 mg/dl) and high small dense LDL-C carries a three-fold higher risk of CHD, especially in women. In view of the above review, mild hypercholesterolemic women included in the present study, had a combination of borderline high serum triglyceride, LDL-C and low HDL-C levels which may increase their susceptibility to CVD risk.

In the premenopausal and postmenopausal test group subjects, there was a significant reduction ($p < 0.001$) in the serum levels of total cholesterol (20.87% and 20.86%), LDL-C (28.57% and 28.95%), VLDL-C (24.13% and 21.30%), triglycerides (24.60% and 22.40%) and serum lipid ratios (total cholesterol: HDL-C, LDL-C:HDL-C, triglycerides: HDL-C), accompanied by a significant ($p < 0.001$) increase in the HDL-C (8.84% and 10.44%) levels after the supplementation period. The Framingham Heart Study and other large scale studies have confirmed a three per cent decrease in CAD risk in women for every mg/dl rise in HDL-C level.

Polyunsaturated omega-3 fatty acids regulate the activity of nuclear receptors, which results in repartitioning of fatty acids away from storage and towards oxidation. This effect is mediated by a reduction in sterol regulatory element-binding protein-1c, the main transcription factor controlling lipogenesis. A reduction in triglyceride synthesis and an increase in hepatic fatty acid oxidation decrease substrate availability for VLDL synthesis and secretion. Triglyceride reduction is also accompanied by an improvement in LPL (lipoprotein lipase) activity and proper maturation of HDL particles. Additionally, upregulation of endogenous apoA-I levels may also account for the increase in HDL cholesterol. Omega-3 PUFA modify the composition of LDL cholesterol by increasing the particle size thus making it less atherogenic.

Elevated serum concentration of CRP is a biomarker for chronic inflammation and a sensitive risk factor for CVD in adults. The mean serum CRP levels of the premenopausal (4.56 ± 0.87) and postmenopausal (4.85 ± 0.83) subjects were greater than 3 mg/L, which according to NCEP, ATP III (2002) [14] may indicate a high risk for CVD. Omega-3 PUFA possess antiinflammatory properties, such as the ability to decrease the production of inflammatory eicosanoids and cytokines, which are inducers of CRP [6]. Physiologically EPA could act as a competitive inhibitor of arachidonic acid conversion to inflammatory mediators (prostaglandin $E_2$ and leukotriene $B_4$). Decreased synthesis of these eicosanoids has been observed after omega-3 fatty acid inclusion in the diet. The mean difference observed in the serum CRP levels between the control and test groups in premenopausal as well as postmenopausal subjects after the study/supplementation period was statistically significant ($p < 0.001$), implying an inverse association of omega-3 PUFA intake with CRP concentration.

## Omega-3 fatty acid supplementation positively impacted the omega-3 index

The omega-3 index which is a new risk marker for CVD correlated negatively with age ($p < 0.01$), obesity indices ($p < 0.01$), dyslipidemia markers ($p < 0.01$), serum CRP concentration ($p < 0.01$), blood pressure levels ($p < 0.01$) and diet-related risk factors including the intakes of energy, total fat, SFA and dietary cholesterol ($p < 0.01$). While serum HDL-C concentration, erythrocyte membrane levels of ALA, EPA, DHA and omega-3 PUFA intake correlated positively ($p < 0.01$) with omega-3 index.

The AA (Arachidonic acid) to EPA ratio is a significant marker of inflammation [12]. AA serves as a biological substrate for the cyclooxygenase and lipoxygenase enzymes, leading to the production of the 2-series prostanoids and the 4-series leukotrienes, exerting a potent proinflammatory effect, whereas EPA gets converted to the anti-inflammatory 3-series prostaglandins and 5-series leukotrienes. Several clinical intervention studies have shown that a reduction in AA to EPA ratio results in an increased protection against heart health disturbances (Simopoulos, 2006).

The sum of EPA and DHA in erythrocyte membranes or the omega-3 index can indicate suboptimal intake of omega-3 fatty acids, which is supposedly a risk factor for CVD. Proposed omega-3 index risk zones for CHD mortality are: high risk, <4 per cent; intermediate risk, 4 to 8 per cent; and low risk, >8 per cent. In the present study, the combined supplementation resulted in a significant increase in the omega-3 index by a mean value of 3.6 accompanied by a reduction in the AA to EPA ratio by a mean value of 1.8 in individuals with a pretreatment omega-3 index of 3.9 and AA to EPA ratio of 3.8.

### Significant findings with regard to blood pressure levels

The mean systolic and diastolic blood pressure levels of the premenopausal (122.3 ± 1.8 and 81.8 ± 2.0) and postmenopausal (127.6 ± 3.2 and 85.0 ± 2.0) subjects in the control and test groups were in the pre-hypertension range (systolic: 120 to 139 mm Hg and/or diastolic: 80 to 89 mm Hg) based on the [17]. In the premenopausal subjects, whose blood pressure levels were slightly above the normal, systolic and diastolic blood pressure levels were lowered (significance level $p < 0.001$) by 1.94% and 2.72% due to the combined supplementation. Whereas in the postmenopausal subjects, whose baseline blood pressure levels were comparatively higher, systolic and diastolic blood pressure levels were reduced (significance level $p < 0.001$) by 4.35% and 5.45% after the supplementation period. The hypotensive effect of flaxseed oil with fish oil may be attributed to the vasodialatory actions, including decreased responsiveness of the vascular system to systemic vasoconstrictors and blood viscosity lowering effect of both the highly unsaturated oils. Additionally, the effect of omega-3 metabolites, prostaglandins on a variety of blood pressure regulators including control of salt and water balance, control of blood flow in the kidneys and effect on cardiac output also underlie the hypotensive effect of omega-3 fatty acids. The Lipid Research Clinical Trial (LRCT) has confirmed that cholesterol abnormalities are four times more common in hypertensive adults than in normotensives. The association between hypertension, CAD and early mortality is stronger in women than in men and there is no threshold below which the risk disappears. Hence, the control of prehypertension in hypercholesterolemic women through a combined supplementation of flaxseed oil with fish oil is of vital importance in reducing the risk of heart disease.

## Conclusion

Upscale your heart health with every form of omega-3 fats! In the present study, the combined supplementation (of plant- and animal-based omega-3 fatty acids, that is, ALA and EPA+DHA) was proven to be significantly hypocholesterolemic, hypotensive, anti-inflammatory and obesity-lowering alongside being cardioprotective in raising the omega-3 index. Regular inclusion of omega-3 fatty acids adequately in the habitual diet appears to be a desirable step in risk reduction, disease prevention and health promotion.

## Conflict of Interest

We hereby declare that we have no conflict of interest of any form pertaining to our research study titled, 'AN UP-TO-DATE MARKER OF HEART HEALTH- THE OMEGA-3 INDEX!'

## Bibliography

1. DiNicolantonio J J and O'Keefe J. "The Importance of Maintaining a Low Omega-6/Omega-3 Ratio for Reducing the Risk of Autoimmune Diseases, Asthma, and Allergies". *Missouri Medicine* 118.5 (2021): 453-459.

2. Bernasconi AA., *et al*. "Omega-3 Benefits Remain Strong Post-STRENGTH". *Mayo Clinic Proceedings* 96.5 (2021): 1371-1372.

3. DiNicolantonio J and O'Keefe J H. "Does Fish Oil Reduce the Risk of Cardiovascular Events and Death? Recent Level 1 Evidence Says Yes: PRO: Fish Oil is Useful to Prevent or Treat Cardiovascular Disease". *Missouri Medicine* 118.3 (2021): 214-218.

4. von Schacky C., *et al*. "Omega-3 fatty acids in heart disease—why accurately measured levels matter". *Netherland Heart Journal* 31 (2023): 415-423.

5. von Schacky C. "Omega-3 index and cardiovascular health". *Nutrients* 6.2 (2014): 799-814.

6. Calder PC. "Mechanisms of Action of (n-3) Fatty Acids". *Journal of Nutrition* 142.3 (2012): 592S-599S.

7. Finnegan YE., *et al*. "Plant and marine-derived n-3 polyunsaturated fatty acids have differential effects on fasting and postprandial blood lipid concentrations and on the susceptibility of LDL to oxidative modification in moderately hyperlipidemic subjects". *American Journal of Clinical Nutrition* 77.4 (2003): 783-95.

8. Goyens PL and Mensink RP. "Effects of alpha-linolenic acid versus those of EPA/DHA on cardiovascular risk markers in healthy elderly subjects". *European Journal of Clinical Nutrition* 60.8 (2006): 978-984.

9. Bowen KJ., *et al*. "Omega-3 Fatty Acids and Cardiovascular Disease: Are There Benefits?". *Current Treatment Options in Cardiovascular Medicine* 18 (2016): 69.

10. Luo Chen., *et al*. "Is Omega-3 Index necessary for fish oil supplements for CVD risk prevention?". *Cardiology Plus* 7.2 (2022): 70-76.

11. Stark KD., *et al*. "Global survey of the omega-3 fatty acids, docosahexaenoic acid and eicosapentaenoic acid in the blood stream of healthy adults". *Progress in Lipid Research* 63 (2016): 132-152.

12. Harris WS., *et al*. "Tissue n-3 and n-6 fatty acids and risk for coronary heart disease events". *Atherosclerosis* 193 (2007): 1-10.

13. Harris S and Falls SD. "The omega-3 index: a new risk factor for death from coronary heart disease". *American Journal of Clinical Nutrition* 87.6 (2008): 1997S-2002S.

14. NCEP ATP III. "National Cholesterol Education Program (NCEP). Executive Summary on the Third report of The National Cholesterol Education Program (ATP III). Expert Panel on Detection, Evaluation and Treatment of high blood cholesterol in adults (Adult Treatment Panel III) Final Report". *Circulation* 106 (2002): 3143-3121.

15. Kris-Etherton P M., *et al*. "Position of the American Dietetic Association and Dietitians of Canada: dietary fatty acids". *Journal of the American Dietetic Association* 107.9 (2007): 1599-1611.

16. Simopoulos AP. "Evolutionary aspects of diet, the omega-6/omega-3 ratio and genetic variation: nutritional implications for chronic diseases". *Biomed Pharmacotherapy* 60.9 (2006): 502-07.

17. WHO. Pan Health Organization (Regional office of WHO). Central America Diabetes Initiative (CAMDI), Survey of Diabetes, Hypertension and Chronic disease risk factors. Villa Nueva, Guatemala (diabetes@paho.org) (2006).