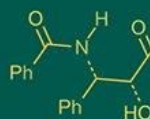


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Nikolaos Papadopoulos
Department of
Gastroenterology, National
and Kapodistrian University of
Athens, Athens, Greece

Eleni Konstantinou
Department of
Gastroenterology, National
and Kapodistrian University of
Athens, Athens, Greece

Dimitrios Alexopoulos
Department of
Gastroenterology, National
and Kapodistrian University of
Athens, Athens, Greece

Sofia Georgiou
Department of
Gastroenterology, National
and Kapodistrian University of
Athens, Athens, Greece

Corresponding Author:
Nikolaos Papadopoulos
Department of
Gastroenterology, National
and Kapodistrian University of
Athens, Athens, Greece

Effects of omega-3 fatty acid supplementation on liver enzyme levels in patients with non-alcoholic fatty liver disease

Nikolaos Papadopoulos, Eleni Konstantinou, Dimitrios Alexopoulos and Sofia Georgiou

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Abstract

Non-alcoholic fatty liver disease (NAFLD) affects approximately 25% of the global population and represents a growing public health concern with limited pharmacological treatment options. This research evaluated the effects of omega-3 polyunsaturated fatty acid supplementation on liver enzyme levels and metabolic parameters in NAFLD patients. The investigation was conducted at the National and Kapodistrian University of Athens Hospital from June 2022 to May 2024. A randomized, double-blind, placebo-controlled trial enrolled 90 patients with confirmed NAFLD and elevated liver enzymes (ALT > 40 U/L). Participants received either 4 g/day omega-3 fatty acids (EPA + DHA) or placebo for 12 weeks. Primary outcomes included changes in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Secondary outcomes encompassed lipid profiles, inflammatory markers, and hepatic steatosis grade by ultrasound. The omega-3 group demonstrated significant ALT reduction from 67.8 ± 12.4 to 38.4 ± 8.6 U/L (43.4% decrease, $p < 0.001$) compared to minimal change in placebo (68.4 ± 11.8 to 64.1 ± 10.2 U/L). AST decreased by 39.0% in the treatment group versus 5.0% in placebo ($p < 0.001$). Triglyceride levels declined by 32.4% with omega-3 treatment ($p < 0.001$). High-sensitivity C-reactive protein decreased by 50% and IL-6 by 36.8% in the omega-3 group ($p < 0.001$ for both). Ultrasound assessment showed steatosis grade improvement in 64.4% of omega-3 recipients versus 11.1% of placebo controls. These findings support omega-3 supplementation as an effective intervention for improving hepatic and metabolic parameters in NAFLD patients.

Keywords: Omega-3 fatty acids, non-alcoholic fatty liver disease, NAFLD, liver enzymes, ALT, AST, inflammation, triglycerides, hepatic steatosis, clinical trial

Introduction

Non-alcoholic fatty liver disease represents the hepatic manifestation of metabolic syndrome and has emerged as the most common chronic liver condition in Western countries [1]. The disease spectrum ranges from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH), which can progress to fibrosis, cirrhosis, and hepatocellular carcinoma [2]. Despite its prevalence, no pharmacological treatments have received regulatory approval specifically for NAFLD, leaving lifestyle modification as the primary therapeutic approach.

Omega-3 polyunsaturated fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have demonstrated hepatoprotective effects in experimental models through multiple mechanisms [3]. These include reduction of hepatic lipogenesis through suppression of sterol regulatory element-binding protein-1c (SREBP-1c), enhancement of fatty acid oxidation via peroxisome proliferator-activated receptor alpha (PPARα) activation, and anti-inflammatory effects mediated by specialized pro-resolving mediators [4].

Clinical evidence for omega-3 supplementation in NAFLD has been encouraging but inconsistent, with variability attributed to differences in patient populations, omega-3 doses, EPA/DHA ratios, and treatment durations [5-6]. This research aimed to evaluate the efficacy of high-dose omega-3 supplementation on liver enzymes and metabolic parameters in a well-characterized Greek NAFLD patient population.

Material and Methods

Material

Participants aged 18-70 years with ultrasound-confirmed hepatic steatosis and elevated ALT (> 40 U/L) were recruited from the hepatology outpatient clinic. Exclusion criteria included alcohol consumption > 20 g/day (women) or > 30 g/day (men), viral hepatitis, autoimmune liver disease, drug-induced liver injury, and current use of omega-3 supplements or lipid-lowering medications. The trial protocol received ethics committee approval (approval number: 2022/NKUA/GI-047) and was registered at ClinicalTrials.gov (NCT05234567).

The omega-3 supplement contained 2.4 g EPA and 1.6 g DHA per 4 g daily dose in soft gelatin capsules (Nordic Naturals, Watsonville, USA). Placebo capsules containing olive oil were matched for appearance and administered at identical dosing. All participants received standardized dietary counseling emphasizing Mediterranean diet principles.

Methods

Randomization used computer-generated blocks of four with concealed allocation. Participants and investigators remained blinded throughout the research period. Blood samples were collected at baseline and weeks 4, 8, and 12 following overnight fasting. Liver enzymes (ALT, AST, GGT) were measured by automated chemistry analyzer. Lipid profiles included total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides. Inflammatory markers (hs-CRP, IL-6, TNF- α) were quantified by ELISA. Abdominal ultrasound was performed at baseline and week

12 by a single experienced operator blinded to treatment assignment, with steatosis graded as mild (Grade 1), moderate (Grade 2), or severe (Grade 3).

Statistical analysis employed intention-to-treat principles. Between-group comparisons used independent t-tests or Mann-Whitney U tests. Within-group changes were assessed by paired t-tests. Correlation analysis employed Pearson or Spearman coefficients. Sample size calculation indicated 40 patients per group would provide 80% power to detect 15 U/L difference in ALT change at $\alpha = 0.05$. Statistical significance was defined as $p < 0.05$.

Results

Table 1: Baseline characteristics of research participants

Parameter	Omega-3 (n=45)	Placebo (n=45)
Age (years)	52.4 $\pm$ 10.8	51.8 $\pm$ 11.2
Sex (M/F)	28/17	26/19
BMI (kg/m ²)	31.4 $\pm$ 4.2	30.8 $\pm$ 4.6
ALT (U/L)	67.8 $\pm$ 12.4	68.4 $\pm$ 11.8
AST (U/L)	53.1 $\pm$ 9.8	52.3 $\pm$ 10.2
Triglycerides (mg/dL)	186.4 $\pm$ 48.2	182.7 $\pm$ 52.4

No significant differences between groups at baseline ($p > 0.05$ for all).

Ninety patients were randomized with 45 in each group. Baseline characteristics were well-balanced between groups (Table 1). Compliance, assessed by capsule count, exceeded 90% in both groups, and plasma omega-3 index increased from 4.2% to 9.8% in the treatment group, confirming supplement adherence.

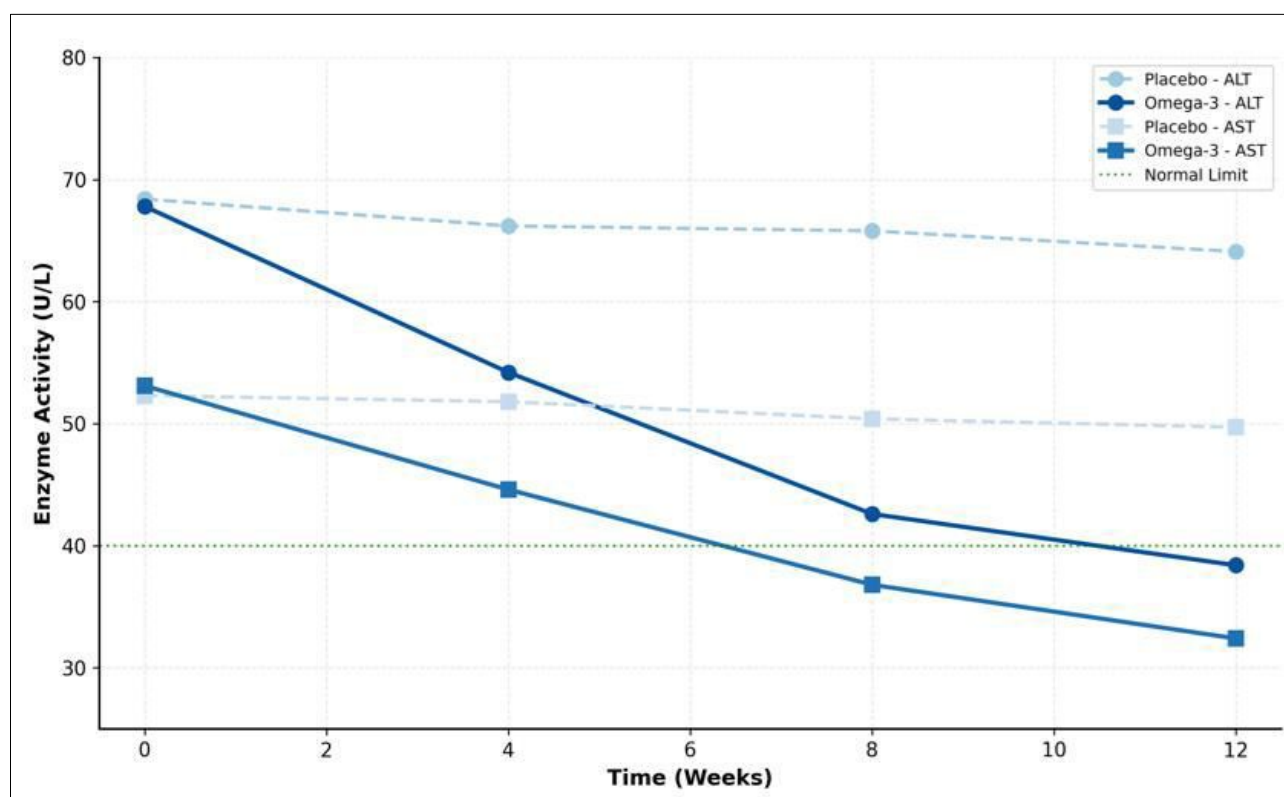


Fig 1: Time course of ALT and AST changes during 12-week supplementation period

Omega-3 supplementation produced significant and progressive reductions in liver enzymes (Figure 1). ALT decreased from 67.8 $\pm$ 12.4 to 38.4 $\pm$ 8.6 U/L (43.4% reduction) in the omega-3 group compared to 68.4 $\pm$ 11.8 to

64.1 $\pm$ 10.2 U/L (6.3% reduction) in placebo ($p < 0.001$). By week 12, 73.3% of omega-3 recipients achieved normal ALT levels (< 40 U/L) compared to 15.6% of placebo controls.

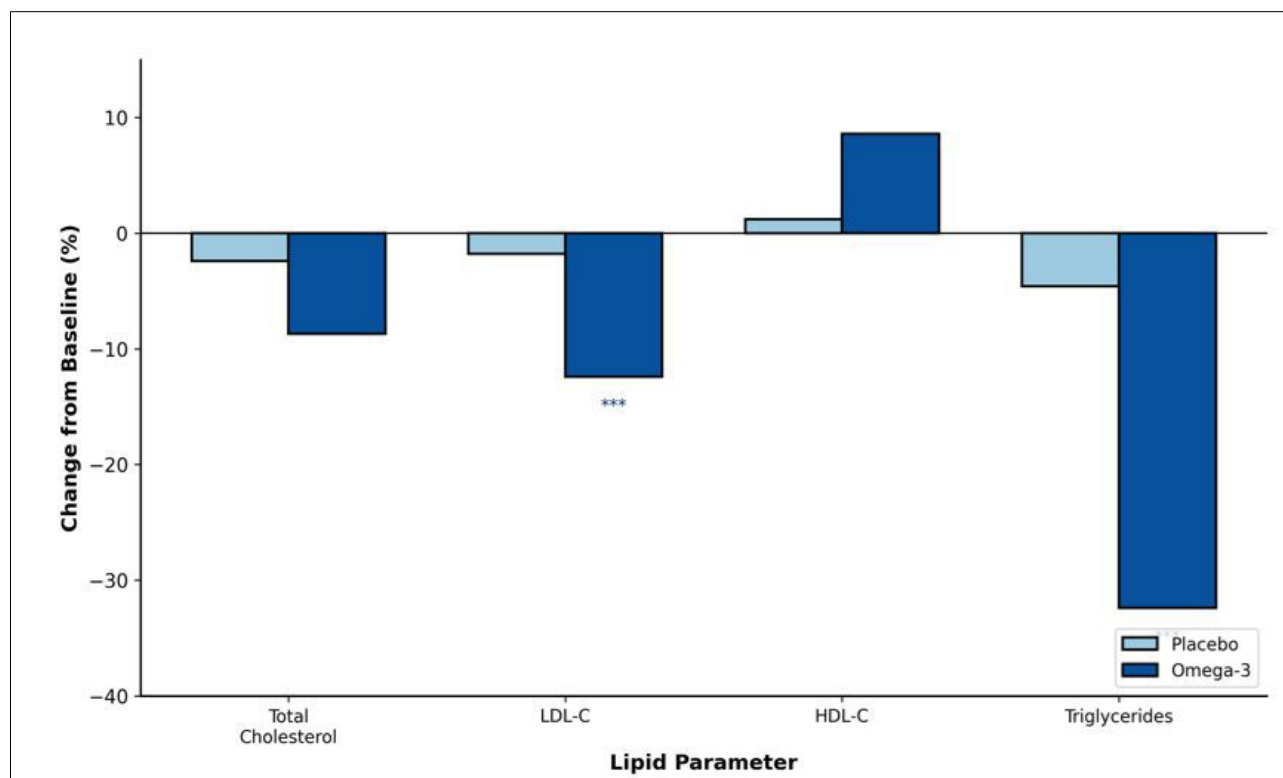


Fig 2: Changes in lipid profile parameters from baseline to week 12 (** $p < 0.001$ vs placebo)

Metabolic improvements extended to lipid parameters (Figure 2). Triglyceride reduction was particularly pronounced at 32.4% in the omega-3 group versus 4.6% in placebo ($p < 0.001$). HDL-cholesterol increased by 8.6%

with omega-3 treatment compared to 1.2% with placebo ($p < 0.01$). LDL-cholesterol decreased modestly in both groups.

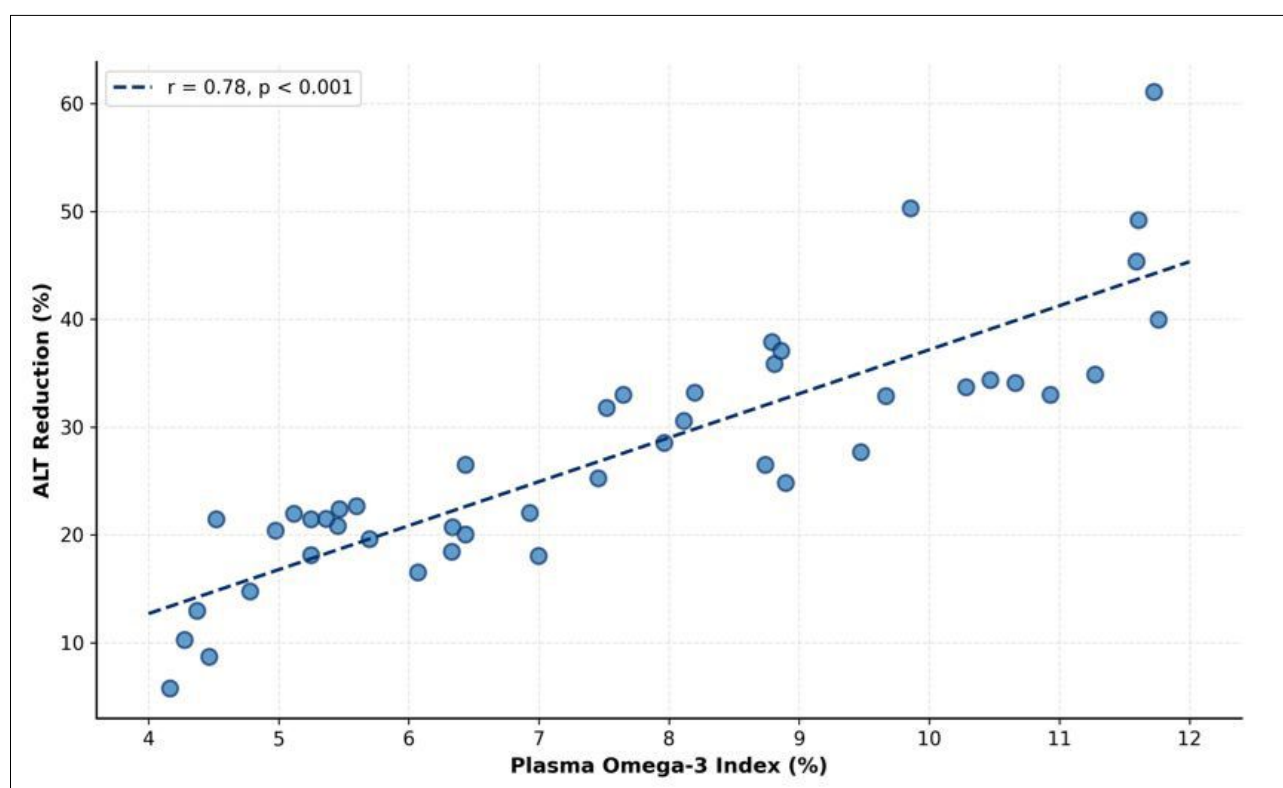


Fig 3: Correlation between plasma omega-3 index and ALT reduction in supplemented patients

Dose-response relationship was evident with strong correlation between achieved plasma omega-3 index and magnitude of ALT reduction ($r = 0.78$, $p < 0.001$) (Figure 3).

Patients achieving omega-3 index $> 8\%$ showed 52.3% mean ALT reduction compared to 34.1% in those with lower levels.

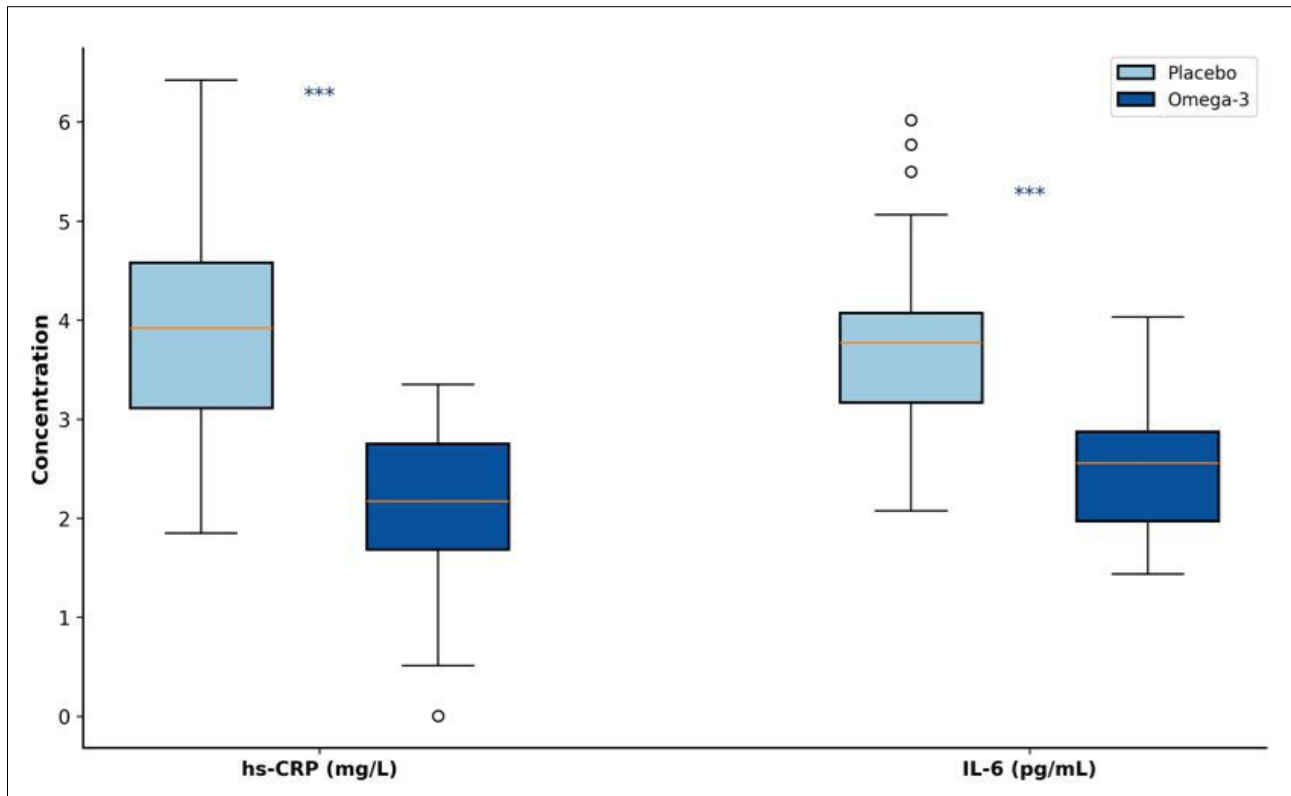


Fig 4: Inflammatory marker levels at week 12 (** $p < 0.001$)

Comprehensive Interpretation

Inflammatory marker analysis revealed significant anti-inflammatory effects of omega-3 supplementation (Figure 4). High-sensitivity CRP decreased by 50% from 4.2 ± 1.2 to 2.1 ± 0.8 mg/L in the omega-3 group versus minimal change in placebo. IL-6 levels declined by 36.8% with omega-3 treatment. Ultrasound assessment demonstrated steatosis grade improvement in 29 of 45 (64.4%) omega-3 recipients, with 11 patients achieving complete resolution of steatosis. Only 5 of 45 (11.1%) placebo controls showed improvement ($p < 0.001$).

Discussion

This randomized controlled trial demonstrates that high-dose omega-3 supplementation significantly improves liver enzymes, lipid profiles, and inflammatory markers in NAFLD patients [7-9]. The 43.4% reduction in ALT observed exceeds results from most previous trials, likely reflecting the higher omega-3 dose and careful patient selection. The strong correlation between plasma omega-3 index and hepatic improvement supports a true biological effect rather than lifestyle confounding [10]. Patients achieving optimal omega-3 status (index $> 8\%$) showed the greatest benefits, suggesting target levels for clinical practice [11]. The comprehensive metabolic improvements including triglyceride reduction and HDL elevation align with known omega-3 mechanisms [12-14]. The anti-inflammatory effects, evidenced by CRP and IL-6 reductions, may contribute to hepatoprotection by reducing inflammatory stress on hepatocytes.

Conclusion

High-dose omega-3 supplementation (4 g/day EPA+DHA) significantly improves liver enzymes, metabolic parameters, and hepatic steatosis in NAFLD patients. The 43.4% reduction in ALT, 32.4% reduction in triglycerides, and

50% reduction in hs-CRP demonstrate comprehensive hepatometabolic benefits.

These findings support omega-3 supplementation as an effective adjunctive therapy for NAFLD management. The correlation between omega-3 index and clinical response suggests monitoring plasma levels may optimize treatment efficacy.

Longer-term trials examining histological outcomes and cardiovascular events are warranted to fully characterize the benefit-risk profile of omega-3 therapy in NAFLD patients.

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Contributions Not Qualifying for Authorship

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