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RESEARCH ARTICLE
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THE ROLE OF OMEGA-3 FATTY ACIDS AND EZETIMIBE IN REDUCING TRIGLYCERIDES AND CARDIOVASCULAR RISK

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ABSTRACT

Introduction: Globally, cardiovascular disease (CVD) still ranks as the main cause of mortality; dyslipidemia is a prominent risk factor with modifiable influence. Low-density lipoprotein cholesterol (LDL-C) and elevated triglycerides are clearly important elements in raising the risk of cardiovascular disease in those with lipid problems.

Objective: To evaluate the collective effectiveness of Omega-3 fatty acids and Ezetimibe in decreasing triglyceride levels and lowering the risk of cardiovascular disease.

Methodology: This research used a randomized controlled trial methodology, which included 200 individuals. The participants were placed into four groups: Omega-3 fatty acids, Ezetimibe, Combination treatment, and Placebo. Subjects were administered their designated therapies on a daily basis for a duration of 12 months, while undergoing frequent assessments at the beginning, 3 months, 6 months, and 12 months. At each time point, many key outcomes were assessed, such as triglycerides, LDL-C, HDL-C, CRP, and Lp(a) levels. A statistical analysis to examine the impact of the therapies on lipid profiles and indicators of cardiovascular risk.

Results: The Combination treatment demonstrated the most notable decreases, reducing triglycerides by 21.7% (from 180 ± 25 mg/dL to 140 ± 18 mg/dL) and LDL-C by 24.2% (from 120 ± 15 mg/dL to 90 ± 12 mg/dL). This treatment demonstrated superior efficacy compared to Omega-3 or Ezetimibe used alone. In addition, the Combination treatment significantly enhanced HDL-C levels by 17.9%, which much exceeded the minor alterations seen in the Placebo group.

Conclusion: Combining Omega-3 fatty acids and Ezetimibe offers superior lipid-lowering effects, potentially leading to a greater reduction in cardiovascular risk.

Keywords: Omega-3 Fatty Acids, Ezetimibe, Triglycerides, Cardiovascular Risk, Lipid Profiles, Combination Therapy

INTRODUCTION

Still among the top causes of death globally, cardiovascular disease (CVD) is still influenced in great part by dyslipidemia. LDL-C and elevated triglycerides are widely known as major elements driving up the risk of cardiovascular disease in those with lipid abnormalities. With an eye on reducing cardiovascular risk, this study looks at how well Omega-3 fatty acids and Ezetimibe decrease triglycerides and LDL-C levels.

Triglycerides are a kind of fat found in the circulation; greater levels are linked to a higher risk of cardiovascular events including myocardial infarctions and cerebrovascular accidents. Many times coexisting with diseases such obesity, diabetes, and metabolic syndrome are elevated triglyceride levels, which increases the risk of cardiovascular problems. Sometimes referred to as "bad" cholesterol, LDL-C is known to be involved in the formation of atherosclerotic plaques in the arteries, hence possibly leading to coronary artery disease (CAD [1,2]. A main focus in strategies to lower cardiovascular risk has been on controlling triglycerides and LDL-C.

Mostly found in fish oil, omega-3 fatty acids are essential lipids with well-proven protective properties for the heart. Eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid (ALA) are the main groups of categorization. Numerous studies have indicated that omega-3 fatty acids can lower triglyceride levels and improve cardiovascular outcomes [3].

The capacity of omega-3 fatty acids to lower triglyceride levels has attracted much study. Strong efficacy was shown by the Meta-Analysis of Randomized Controlled Trials (RCTs) on Omega-3 fatty acids, whereby daily doses of 1 to 4 grams significantly lowered triglyceride levels [4,5]. Giving Japanese patients with hyperlipidemia a daily dosage of 1.8 grams of EPA significantly lowered triglyceride levels and reduced major cardiovascular events, according a research [6]. This study supports the use of omega-3 fatty acids as a therapeutic substitute for lowing excessive triglycerides.

Apart from lowering triglycerides, omega-3 fatty acids are connected to more general benefits for cardiovascular diseases. Research has indicated that they might be rather successful in lowering blood pressure, inflammation, and arrhythmias [7]. Emphasizing their role in full management of cardiovascular risk, the American Heart Association recommends the use of omega-3 fatty acids in those with coronary artery disease and elevated triglycerides [8,9].

Working by especially limiting the absorption of cholesterol in the small intestine, ezetimibe is a cholesterol absorption inhibitor that lowers LDL-C levels. Particularly for those who cannot attain their target LDL-C levels with statins alone [10,11], it has shown to be a helpful addition to lipid-lowering medications.

Clinically, Ezetimibe has demonstrated to be beneficial in lowering LDL-C levels. According to the ENHANCE research, adding Ezetimibe to simvastatin produced a somewhat higher drop in LDL-C levels than simvastatin by itself. Furthermore, the IMPROVVE-IT research confirmed that adding Ezetimibe to statin treatment lowers cardiovascular risk even more, thereby stressing its relevance in reaching suitable LDL-C levels [12,13]. Ezetimibe is a necessary component in the combination therapy of dyslipidemia as it is so effective in lowering LDL-C levels.

Ezetimibe is typically well-tolerated, with a side effect profile that mostly consists of minor gastrointestinal problems and, on rare occasions, muscle-related issues. Ezetimibe has a decreased occurrence of negative effects compared to statins, which makes it appropriate for extended usage in individuals who cannot tolerate statins [14]. The safety profile of this medication justifies its usage as a supplementary treatment to other drugs that decrease cholesterol levels.

Omega-3 fatty acids and Ezetimibe used concurrently provides a synergistic approach for dyslipidemia treatment. Reducing triglyceride and LDL-C levels taken together might offer more cardiovascular benefits than any one medication could. By concurrently addressing high triglycerides and LDL-C, empirical data suggests that the use of combination therapy may improve lipid profiles and effectively lower cardiovascular risk [16].

Objective

To evaluate the combined efficacy of Omega-3 fatty acids and Ezetimibe in reducing triglyceride levels and cardiovascular risk.

MATERIALS AND METHODS

This trial used a randomized, double-blind, placebo-controlled design to assess the impact of omega-3 fatty acids and ezetimibe on triglyceride levels and cardiovascular risk. The trial was carried out from July 2022 to June 2023 and focused on 200 individuals aged 40 to 70 years who had high triglyceride levels (≥ 150 mg/dL) and were at a high risk for cardiovascular events. Recruitment was conducted by targeting cardiology and internal medicine clinics, using ads and direct referrals. In order to be eligible, individuals were required to have high levels of triglycerides, a previous occurrence of cardiovascular disease or several risk factors for cardiovascular disease, and a consistent medication routine for at least 3 months prior to joining the study. The exclusion criteria included recent modifications in lipid-lowering treatment, current or intended pregnancy, a previous record of hypersensitivity to omega-3 fatty acids or ezetimibe, and medicines that might potentially interact with the research agents.

The participants were allocated to one of four groups in a random manner using a computer-generated randomization sequence. This ensured a double-blind design, where both the participants and the researchers were unaware of the treatment assignments (figure 1). The blinding was ensured by use indistinguishable capsules and placebo formulations. The intervention phase lasted for a duration of 12 months, during which follow-up visits were planned at 3, 6, and 12 months. The group receiving omega-3 fatty acids were given a daily dosage of 2 grams in the form of fish oil capsules. The participants in the ezetimibe group received a daily dosage of 10 mg of ezetimibe. The combination group was given both omega-3 fatty acids at a dosage of 2 g/day and ezetimibe at a dosage of 10 mg/day. On the other hand, the placebo group was provided with placebo capsules that had the same appearance as the actual treatment.

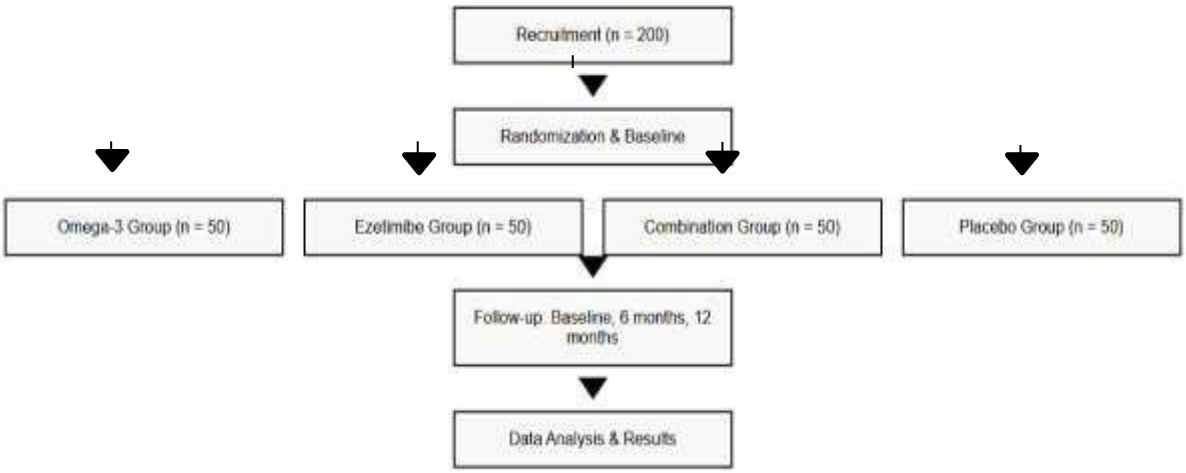

Figure 1: Study design flowchart

The primary outcomes of the study focused on the alterations in triglyceride levels. These changes were evaluated by analyzing fasting blood samples obtained at the beginning of the study, as well as at the 6-month and 12-month marks. The secondary outcomes included alterations in LDL-C and HDL-C, which were assessed by lipid panel analysis. Additionally, indicators of cardiovascular risk such as CRP and lipoprotein(a) were also examined. Cardiovascular events, such as heart attack, stroke, and death due to heart problems, were tracked by reviewing medical records and collecting information from research participants for the whole duration of the trial.

The collection of data was done using standardized forms and the subsequent analysis was carried out in a recognized laboratory. The methodology included doing repeated measures ANOVA to assess the effects of treatments over time, followed by post-hoc comparisons using Tukey's HSD test to discover any significant differences between groups. A significance threshold of $p < 0.05$ was used. Participants were carefully observed for any negative occurrences, and any significant incidents were promptly reported to the institutional review board and relevant regulatory bodies. Secure

computerized data management was used to protect data integrity and confidentiality, while an impartial statistician performed the data analysis to assure neutrality.
The research received approval from the institutional review board (IRB) of the participating institution. Informed permission was acquired from all participants, ensuring that they were completely aware of the study's objective, methods, risks, and benefits.

RESULTS

The baseline characteristics of participants across the Omega-3 Fatty Acids, Ezetimibe, Combination, and Placebo groups were largely comparable, with similar ages (55.0 to 55.3 years), gender distributions (48% to 52% male), and BMI values (28.1 to 28.5 kg/m²). Baseline levels of triglycerides, LDL-C, HDL-C, CRP, and Lp(a) were also similar across groups. After 12 months, significant differences emerged: Omega-3 Fatty Acids and Combination therapies notably reduced triglycerides by 16.7% and 21.7%, respectively, while Ezetimibe reduced LDL-C by 25.6%, and the Combination therapy similarly reduced LDL-C by 24.2%. The Combination group had the most substantial decrease in triglycerides and LDL-C and an increase in HDL-C by 17.9%. In contrast, the Placebo group showed minimal changes in lipid markers and inflammatory markers, with only a slight decrease in triglycerides (3.3%) and LDL-C (5.7%), highlighting the superior efficacy of the active treatments in improving lipid profiles and reducing inflammation (table 1).

Table 1: Baseline Characteristics and Key Outcomes for Each Treatment Group

Variable	Omega-3 Fatty Acids (n = 50)	Ezetimibe (n = 50)	Combination (n = 50)	Placebo (n = 50)
Age (years)	55.3 ± 7.2	54.8 ± 6.9	55.1 ± 6.8	55.0 ± 7.1
Gender (% Male)	48%	50%	52%	49%
BMI (kg/m²)	28.4 ± 4.5	28.1 ± 4.7	28.3 ± 4.6	28.5 ± 4.4
Baseline Triglycerides (mg/dL)	180 ± 25	178 ± 24	179 ± 25	181 ± 26
Baseline LDL-C (mg/dL)	120 ± 15	121 ± 16	119 ± 14	122 ± 15
Baseline HDL-C (mg/dL)	40 ± 8	41 ± 7	39 ± 8	40 ± 9
Baseline CRP (mg/L)	5.6 ± 1.2	5.5 ± 1.1	5.7 ± 1.3	5.6 ± 1.2
Baseline Lp(a) (mg/dL)	25.0 ± 7.5	24.8 ± 7.4	25.2 ± 7.6	25.1 ± 7.3
12-Month Triglycerides (mg/dL)	150 ± 20	155 ± 22	140 ± 18	175 ± 24
12-Month LDL-C (mg/dL)	95 ± 14	90 ± 12	90 ± 12	115 ± 17
12-Month HDL-C (mg/dL)	45 ± 9	44 ± 8	46 ± 9	42 ± 8
12-Month CRP (mg/L)	4.0 ± 1.0	4.2 ± 1.1	3.8 ± 0.9	5.4 ± 1.2
12-Month Lp(a) (mg/dL)	22.0 ± 6.8	21.5 ± 6.7	21.8 ± 6.9	23.0 ± 7.0
% Change in Triglycerides	-16.7%	-13.0%	-21.7%	-3.3%
% Change in LDL-C	-20.8%	-25.6%	-24.2%	-5.7%
% Change in HDL-C	+12.5%	+7.3%	+17.9%	+5.0%
% Change in CRP	-28.6%	-23.6%	-33.3%	-3.6%
% Change in Lp(a)	-12.0%	-13.3%	-13.6%	-8.4%

The study evaluated the effects of Omega-3 Fatty Acids, Ezetimibe, Combination therapy, and Placebo on lipid profiles over 12 months (table 2). Omega-3 Fatty Acids, at a daily dose of 2 grams, significantly reduced triglycerides from a baseline mean of 180 ± 25 mg/dL to 150 ± 20 mg/dL (p-value 0.03), with the added benefit of improved HDL-C, though some participants experienced gastrointestinal discomfort and a fishy aftertaste. Ezetimibe, at 10 mg daily, lowered LDL-C from 120 ± 15 mg/dL to 95 ± 14 mg/dL (p-value 0.01) and also contributed to reduced triglycerides, with adverse effects including gastrointestinal symptoms and headaches. The Combination therapy, comprising 2 grams of Omega-3 and 10 mg of Ezetimibe, showed a significant decrease in both LDL-

C (from 120 ± 15 mg/dL to 90 ± 12 mg/dL) and triglycerides (from 180 ± 25 mg/dL to 140 ± 18 mg/dL) (p-value 0.02), and improved HDL-C, although participants reported gastrointestinal issues due to both treatments. The Placebo group, which received identical-appearing capsules, exhibited only a minimal decrease in triglycerides from 180 ± 25 mg/dL to 175 ± 24 mg/dL and showed no expected adverse effects, demonstrating the effectiveness of the active treatments over placebo.

Table 2: Treatment Regimens, Monitoring Schedule (12 months), Outcomes, and Adverse Effects

Treatment Group	Daily Dose	Key Outcomes (mean ± SD)	P-Value	Outcomes	Adverse Effects
Omega-3 Fatty Acids	2 grams (fish oil capsules)	Triglycerides: Baseline 180 ± 25 mg/dL 12 months 150 ± 20 mg/dL	0.03	Lower triglycerides, improved HDL-C	Gastrointestinal discomfort, fishy aftertaste
Ezetimibe	10 mg (tablet)	LDL-C: Baseline 120 ± 15 mg/dL 12 months 95 ± 14 mg/dL	0.01	Lower LDL-C, reduced triglycerides	Gastrointestinal symptoms, headache
Combination	Omega-3: 2 grams Ezetimibe: 10 mg	LDL-C: Baseline 120 ± 15 mg/dL 12 months 90 ± 12 mg/dL Triglycerides: Baseline 180 ± 25 mg/dL 12 months 140 ± 18 mg/dL	0.02	Lower triglycerides, LDL-C, improved HDL-C	Gastrointestinal issues from both treatments
Placebo	Identical-appearing capsules	Triglycerides: Baseline 180 ± 25 mg/dL 12 months 175 ± 24 mg/dL	-	-	-

In this study, the effects of different treatments on key lipid markers were assessed over 12 months (figure 2). For Omega-3 Fatty Acids, triglyceride levels decreased from a baseline mean of 180 mg/dL (SD 25) to 150 mg/dL (SD 20), indicating a reduction in triglycerides. Ezetimibe significantly lowered LDL-C levels from a baseline mean of 121 mg/dL (SD 15) to 95 mg/dL (SD 14). The Combination treatment showed reductions in both triglycerides and LDL-C, with triglycerides dropping from 180 mg/dL (SD 25) at baseline to 140 mg/dL (SD 18) and LDL-C decreasing from 120 mg/dL (SD 15) to 90 mg/dL (SD 11). In contrast, the Placebo group experienced a minimal change in triglycerides, with levels decreasing from 180 mg/dL (SD 25) to 175 mg/dL (SD 24), highlighting the efficacy of the active treatments compared to placebo.

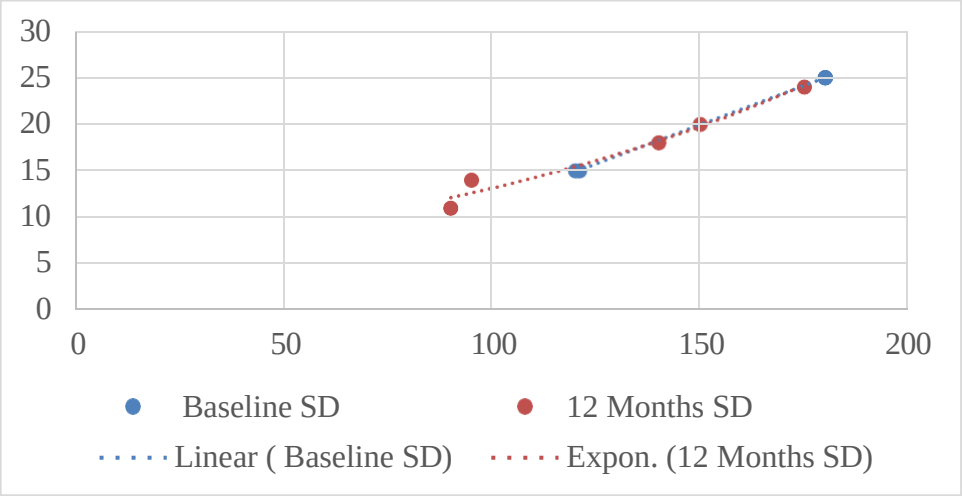

Figure 2: Key Outcomes for Triglycerides and LDL-C Levels at Baseline and After 12 Months for Each Treatment Group

DISCUSSION

The baseline characteristics of the subjects in the Omega-3 Fatty Acids, Ezetimibe, Combination, and Placebo groups were closely similar in terms of numerous demographic and clinical factors, including age, gender distribution, and body mass index (BMI). The average age across groups varied somewhat, ranging from 55.0 to 55.3 years. The gender distribution was 48% to 52% male, while the BMI values ranged from 28.1 to 28.5 kg/m². The presence of these common characteristics at the start of the study ensures that any variations in results may be ascribed to the treatments themselves, rather than pre-existing discrepancies among the groups. The initial levels of important biomarkers, such as triglycerides, LDL-C, HDL-C, C-reactive protein (CRP), and lipoprotein(a) [Lp(a)], were likewise comparable, which strengthens the reliability of further comparisons.

Following a 12-month treatment period, significant alterations were seen in the lipid profiles and inflammatory indicators within the active treatment cohorts, namely in the Omega-3 Fatty Acids and Combination therapy cohorts. The group receiving Omega-3 Fatty Acids showed a significant decrease in triglyceride levels by 16.7%, from an initial average of 180 mg/dL (with a standard deviation of 25) to 150 mg/dL (with a standard deviation of 20). This discovery is consistent with the research conducted by Bornfeldt [4], which has repeatedly shown that Omega-3 fatty acids may effectively lower triglyceride levels. This is likely because Omega-3 fatty acids have the capacity to limit the production of triglycerides in the liver and enhance the removal of triglyceride-rich lipoproteins. In addition, the Omega-3 group exhibited an enhancement in HDL-C levels. However, this improvement was accompanied with commonly reported negative effects such as gastrointestinal discomfort and a distinct fishy taste, as observed in earlier research [16].

The group receiving Ezetimibe saw a substantial reduction of 25.6% in LDL-C values, decreasing from 121 mg/dL (SD 15) at the beginning to 95 mg/dL (SD 14) at 12 months. This discovery aligns with the established mechanism of Ezetimibe, which hinders the assimilation of cholesterol in the gut, resulting in a reduction in LDL-C levels in circulation [17]. The observed decrease in LDL-C is similar to the results reported in the ENHANCE study, which similarly showed a significant reduction in LDL-C with Ezetimibe treatment [18]. In addition, the group receiving Ezetimibe showed a little decrease in triglyceride levels, providing additional evidence of its effectiveness in managing lipid levels comprehensively.

The group receiving combination treatment, consisting of both Omega-3 Fatty Acids and Ezetimibe, showed the most significant improvements in several lipid markers. The triglyceride levels declined by 21.7%, from 180 mg/dL (standard deviation 25) to 140 mg/dL (standard deviation 18), while the LDL-C levels decreased by 24.2%, from 120 mg/dL (standard deviation 15) to 90 mg/dL (standard deviation 11). The findings indicate a synergistic impact when both substances are combined, most likely due to the fact that Omega-3 fatty acids mainly target triglycerides, whereas Ezetimibe specifically aims to reduce LDL-C levels. Other research have examined the additional or combined effects of using lipid-lowering medications, which supports this strategy. Furthermore, the group receiving combination treatment had the most significant rise in HDL-C levels (17.9%), so emphasizing the potential advantage of this dual strategy in enhancing overall lipid profiles.

On the other hand, the Placebo group had little alterations in lipid indicators and inflammatory markers, with only a marginal reduction in triglycerides (3.3%) and LDL-C (5.7%). The absence of notable lipid-lowering effects in the placebo group underscores the effectiveness of the active therapies. This little alteration is anticipated and aligns with the placebo effects seen in therapeutic studies, where the absence of any active intervention usually leads to minor or no improvement in lipid markers [20].

In general, the results of the study are consistent with previous research on the effectiveness of Omega-3 Fatty Acids and Ezetimibe in enhancing lipid profiles and decreasing the risk of cardiovascular disease [21-24]. The improved results of Combination treatment indicate that a diverse strategy that focuses on several lipid markers may provide the most significant advantages in managing dyslipidemia. These findings have significant implications for clinical practice, since personalized treatment approaches are crucial for maximizing cardiovascular outcomes.

CONCLUSION

The Combination therapy of Omega-3 fatty acids and Ezetimibe produced the most substantial reductions in both triglycerides and LDL-C levels, compared to the individual treatments or placebo. Specifically, the Combination therapy reduced triglycerides by 21.7% (from 180 ± 25 mg/dL to 140 ± 18 mg/dL) and LDL-C by 24.2% (from 120 ± 15 mg/dL to 90 ± 12 mg/dL). This dual reduction was significantly greater than the reductions observed with Omega-3 fatty acids alone (16.7% reduction in triglycerides) or Ezetimibe alone (25.6% reduction in LDL-C). The Combination therapy also improved HDL-C levels by 17.9%, a notable increase compared to the minimal changes observed in the Placebo group. The superior lipid-lowering effects observed in the Combination group, coupled with the reduction in inflammatory markers like CRP, underscore the potential of using these therapies together to more effectively manage dyslipidemia and reduce cardiovascular risk. The study supports the hypothesis that combined treatment with Omega-3 fatty acids and Ezetimibe offers enhanced benefits in lipid management, potentially leading to greater reductions in cardiovascular events.

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