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Meta-analysis

Effect of omega-3 fatty acid supplementation on markers of inflammation and endothelial function in patients with chronic heart disease: A systematic review and meta-analysis

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Abstract

Chronic heart disease (CHD) is still a major global cause of morbidity and mortality, necessitating effective therapeutic interventions to mitigate its progression. Omega-3 fatty acids (FAs) have garnered attention for their potential anti-inflammatory and endothelial-protective properties in CHD management. The present study aims to assess the efficacy of Omega-3 FA supplementation on markers of inflammation and endothelial function in patients with CHD. To achieve this, we used the relevant keywords to search international databases (Web of Science, PubMed, Embase, and Scopus) and extract publications evaluating the effectiveness of omega-3 FA supplementation on inflammation markers and endothelial function in patients with CHD. STATA (version 15) and the random and fixed-effects models were used to evaluate the collected data. Thirteen clinical trial studies met inclusion criteria, with a total sample size of 853 individuals (406 cases and 447 controls). The cases had a mean age of 58 ± 10.3 years. The pooled results indicated that omega-3 Omega-3 FA supplementation significantly reduced the level of circulating IL-6 (SMD = -0.47, 95% CI -1.29 to 0.35, %, $p < 0.001$), hs-CRP (SMD = -0.21, 95% CI -0.70 to 0.28, $p = 0.01$), and TNF-α (SMD = -0.56, 95% CI -1.14 to 0.01, $p < 0.001$) in patients with CHD. Also, findings revealed that a daily supplement of omega-3 significantly increased FMD by 0.34% (95% CI: 0.14–0.54%, $p < 0.001$) as compared with placebo by a fixed-effect model in patients with CHD. These findings underscore the potential therapeutic utility of omega-3 fatty acid supplementation in modulating inflammation and endothelial dysfunction in patients with CHD.

Keywords: Omega-3 fatty acids, Supplementation, Inflammation, Endothelial function, Chronic heart disease.

1. Introduction

Chronic heart disease (CHD) represents a significant global health burden, contributing substantially to morbidity and mortality rates worldwide [1]. Understanding the complex mechanisms behind CHD's etiology and developing therapeutic strategies to slow the disease's progression has received a lot of interest in the effort to mitigate its negative consequences. Of the many variables related to CHD, endothelial dysfunction and inflammation have been identified as critical players that accelerate atherosclerosis forward and cause subsequent cardiovascular events [2].

The possible therapeutic role of omega-3 fatty acids (FAs), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), in regulating inflammation and endothelial function in patients with CHD has garnered increasing attention in recent years [3]. Essential polyunsaturated fats and omega-3 FAs are mostly found in fatty fish and some plant sources. Studies investigating the mechanistic functions and clinical efficacy of omega-3 FAs in managing CHD consistently demonstrate a negative correlation between the intake of these lipids and the susceptibility to cardiovascular disorders [4].

The pathophysiology of atherosclerosis involves an inflammatory cascade that begins with endothelial dysfunction and ends with the development of atherosclerotic plaques and thrombotic events [5]. It has been demonstrated that omega-3 FAs have anti-inflammatory properties via a variety of pathways, such as the inhibition of pro-inflammatory cytokine production, immune cell function modulation, and modification of lipid mediator profiles [6]. Omega-3 FAs can decrease endothelial dysfunction, decrease plaque instability, and confer cardiovascular protection in individuals with CHD. by decreasing the inflammatory response [7].

Recent research suggests a correlation between omega-3 intake and enhanced endothelial function [8, 9]. Omega-3 FAs may enhance endothelial function by mitigating the synthesis of inflammatory cytokines and fostering endothelium-dependent vasodilation through increased nitric oxide release [10]. Flow-mediated dilation (FMD) serves as a noninvasive measure of endothelial function and is commonly utilized to assess endothelium-dependent vasodilation in humans [11]. A lower FMD value suggests endothelial dysfunction and has been correlated to a higher risk of cardiovascular events. Conversely, endothelium-

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independent vasodilation (EIV) can be assessed using sublingual nitroglycerin to ascertain whether the dilation is endothelium-induced [12].

Despite increasing evidence from observational and preclinical research that omega-3 FAs have anti-inflammatory and endothelial-protective characteristics [13, 14], the outcomes of clinical trials investigating their effectiveness in individuals with CHD have yielded mixed results. Various trial designs, patient populations, dosages, treatment durations, and outcome measures can all contribute to inconsistent results. Therefore, this study endeavor to enhance our understanding of the role of omega-3 FAs in CHD management by shedding light on their impacts on inflammation markers and endothelial function. The results of this study could have significant implications for optimizing cardiovascular health and reducing the burden of CHD-related complications in affected individuals.

2. Materials and Methods

This systematic review was undertaken to examine the existing evidence, and our findings are outlined according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [15].

2.1. Search strategy

To retrieve the published studies on the impact of omega-3 FA supplementation on endothelial function and inflammatory markers in CHD patients, a thorough search was conducted. The keywords used included “Omega-3 fatty acids”, “supplementation”, “inflammation”, “endothelial function”, “chronic heart disease,” and “flow-mediated dilation”. Various combinations of these keywords and Boolean operators ("OR" and "AND”) were used to search international databases, such as ISI, PubMed, Embase, and Scopus. In order to locate studies that weren't in the databases above, Google Scholar was also searched. Additionally, potentially relevant papers were found by looking through the extracted studies' references. The endnote was then imported with all the records. Records that were duplicated were then removed. We also checked the reference list of concerned articles and searched Google Scholar as grey literature to prevent missing any eligible studies.

2.2. Inclusion and exclusion criteria

The following criteria guided the inclusion of studies in our systematic review and meta-analysis: 1) original articles written in English, 2) studies investigating the effect of omega-3 FA supplementation on markers of inflammation and endothelial function, 3) participants diagnosed with chronic heart disease, and 4) randomized controlled trials (RCTs), observational studies, and clinical trials.

We excluded 1) review articles, editorial articles, and book chapters, and 2) participants without chronic heart disease, non-human studies, 3) studies without clear reporting of relevant outcome measures, 4) research articles written in languages other than English. The flow diagram (Fig. 1) shows the studies selected in this study.

2.3. Risk of bias in individual studies (Quality assessment)

The Newcastle-Ottawa scale (NOS) [16] was used to assess the risk of bias in individual investigations. Case-control and cohort studies scored 9 points, indicating good quality and low risk of bias: The quality ratings for studies 1-3, 4-6, and 7-9 were low, moderate, and high, respectively (Table 1).

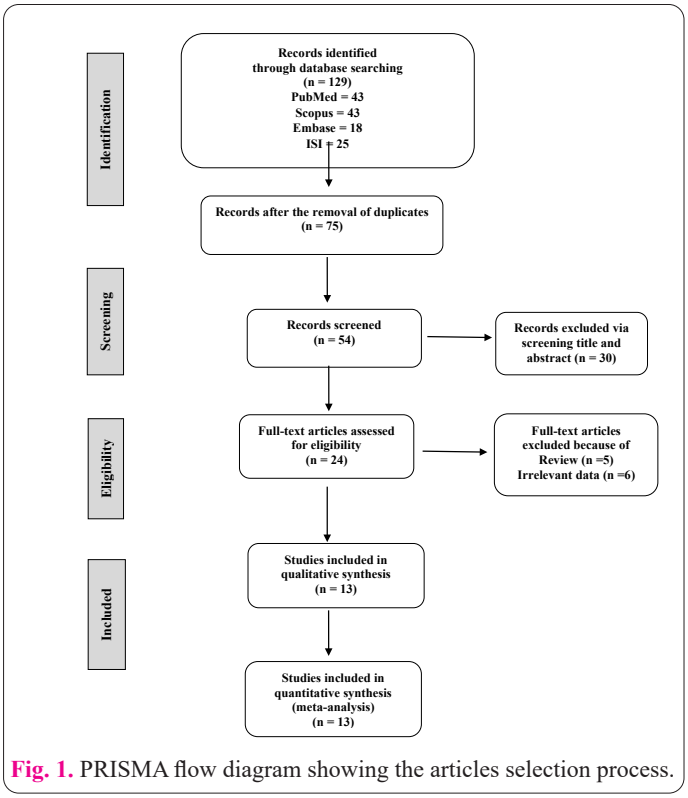

Fig. 1. PRISMA flow diagram showing the articles selection process.

2.4. Data extraction

Data were retrieved by two independent authors from selected publications. The relevant data, such as the first author's name, the location, and the year of publication, sample size, mean age, and design of the study. Also, we mentioned the Omega-3 dose (g/day) and duration of intervention, mean ± SD of interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-α) levels, and FMD in placebo and intervention groups. After being checked by other authors for possible errors, the data were verified by all authors.

2.5. Risk of bias across studies

The Egger test and Begg's Funnel plots assessed the publication bias. P values under 0.05 were taken into consideration for heterogeneity.

2.5. Statistical analysis

The sample size, mean, and standard deviation of the anticipated data were among the variables that were grouped. We allocated a weight to each study according to its inverse variance. Test heterogeneity among included studies was assessed using the I^2 index and Q test at a significance-level error of less than 10%. The analysis of heterogeneous data was done using the random effect model. All of the data was also analyzed using Stata 15.

3. Results

After removing duplicate and irrelevant studies, finally, thirteen clinical trial articles aligned with the inclusion criteria, published between 2006 and 2021, were incorporated into the study. The steps of selecting the studies are shown in Figure 1. A total of 853 subjects were examined (including 406 subjects in intervention group). The Mean

Table 1. Characteristics of the research that this study reviewed.

Author Ref	Year	Country	Total Sample Size/ Intervention	Male	Age (Mean±SD)	Study design	Intervention/ Control	Omega-3 dose (g/day)	Duration	Quality assessment Total score
O'Keefe [17]	2006	USA	18/9	18	-	Randomized, double-blind, placebo-controlled, crossover trial	EPA and DHA/ Placebo	0.585	4	5
Mehra [18]	2006	USA	14/7	10	57±12	Randomized Double-blind, placebo-controlled, crossover trial	44% EPA, 24% DHA, 12% other n-3 fatty acid ethyl esters / iso-caloric corn oil placebo	8	4.5	6
ZHAO [19]	2009	China	75/38	53	74±6	Randomized Double-blind, placebo-controlled, crossover trial	EPA and DHA/ Placebo	2	3	8
Eschen [20]	2010	Italy	138/69	118	58±1	Randomized, double-blind, placebo-controlled, multicenter trial	EPA and DHA/ Placebo	1	6	5
Nodari [21]	2011	USA	133/66	120	64±9	Randomized Double-blind, placebo-controlled, 2-arm design	EPA and DHA/ Placebo	2	12	6
Eftekhari [22]	2013	Iran	87/30	39	54.53±15.12	Randomized Double-blind, placebo-controlled, 2-arm design	EPA and DHA/ Placebo	3	2	8
Grenon [23]	2015	USA	80/40	39	68±7	Randomized, double-blinded, and placebo-controlled trial.	EPA and DHA/ Placebo	4.4	1	7
Mizia-Stec [24]	2011	Poland	38/19	30	56±8	Single-blinded, randomized controlled study	EPA and DHA/ standard therapy	1.8	3	8
Casanova [25]	2017	Brazil	29/13	17	54±1	Single-blinded, randomized controlled study	EPA and DHA/ Ciprofibrate	1.8	3	7
Sawada [26]	2016	Japan	107/54	87	68.9±8.8	Single-blinded, randomized controlled study	EPA/Placebo	1.8	6	7
Oikonomou [27]	2019	USA	31/17	21	67±6	Randomized Double-blind, placebo-controlled, cross-over trial	EPA and DHA/ Placebo	2	2	8
Moertl [28]	2011	Italy	43/14	37	58.6±7	Double-blind, randomized, controlled pilot trial	EPA and OFA (omega-3 series polyunsaturated fatty acids)/ Placebo	1 4	3	7
Yuan [29]	2021	China	60/30	54	58.5±13.3	Single-center, two-aimed randomized	EPA and DHA/ standard therapy	2	3	6

± SD age of the investigated subjects was 58 ± 10.3 years (Table 1).

3.1. Impacts of omega-3 FA supplementation on IL-6 in CHD

Five trials [17, 19, 21–23] reported the effects of omega-3 FA supplementation on IL-6 in CHD. These studies showed significant heterogeneity ($I^2 = 93.03\%$, $p < 0.001$). The combined findings showed that in patients with CHD, omega-3 FA supplementation significantly decreased the level of circulating IL-6 (SMD = -0.47, 95% CI -1.29 to 0.35, %, $p < 0.001$: Figure 2).

3.1. Impacts of omega-3 fatty acid supplementation on hs-CRP in CHD

Four studies [17, 19, 22, 23] reported the impacts of

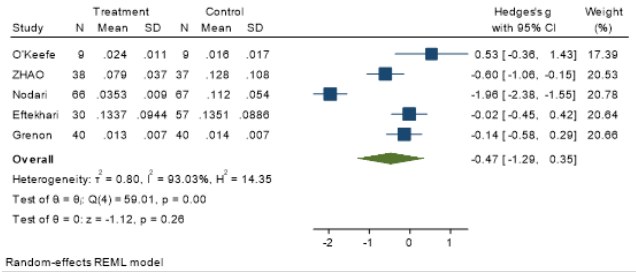

Fig. 2. Forest plots of the effect of omega-3 FA supplementation on IL6 in CHD across the included studies are presented, with 95% CI calculated based on a random model. In the graphical representation, each square symbolizes the effect estimate from each study, with squares greater than the 95% confidence interval. The weights given to each study in the meta-analysis are reflected in the size of the squares. The total estimate is shown by a diamond.

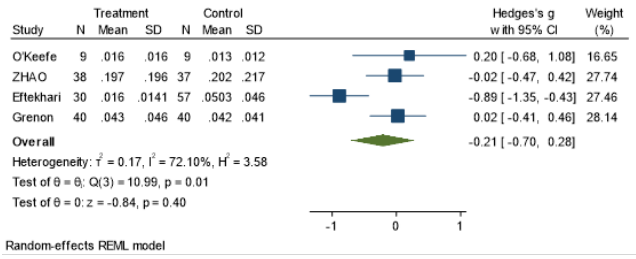

Fig. 3. Forest plots of the effect of omega-3 FA supplementation on hsCRP in CHD across the included studies are presented, with 95% CI calculated based on a random model. In the graphical representation, each square symbolizes the effect estimate from each study, with squares greater than the 95% confidence interval. The weights given to each study in the meta-analysis are reflected in the size of the squares. The total estimate is shown by a diamond.

omega-3 FA supplementation on hs-CRP in CHD patients. These trials showed significant heterogeneity ($I^2 = 72.10\%$, $p = 0.01$). According to the combined data, individuals with CHD had a substantial decrease in level of hs-CRP (SMD = -0.21, 95% CI -0.70 to 0.28, p = 0.01: Figure 3) after taking omega-3 FA supplements.

3.1.1. Impacts of omega-3 fatty acid supplementation on TNF-α in CHD

Five studies [17–19, 21, 23] reported the effects of omega-3 FA supplementation on TNF-α in CHD patients. The aggregated results showed that omega-3 FA supplementation significantly decreased the level of circulating TNF-α in patients with CHD (SMD = -0.56, 95% CI -1.14 to 0.01, $p < 0.01$: Figure 4). Significant heterogeneity was detected among these trials ($I^2 = 81.42\%$, $p < 0.001$).

3.1.2. Effects of omega-3 fatty acid supplementation on FMD in CHD

Seven studies [23–29] reported the effects of omega-3 FA supplementation on FMD in CHD patients. Between these investigations, there was no significant heterogeneity ($I^2 = 30.98\%$, $p = 0.19$). Using a fixed-effect model (Figure 5), the pooled data demonstrated that a daily omega-3 supplement significantly increased FMD by 0.34% (95% CI: 0.14–0.54%, $p < 0.001$) in patients with CHD when compared with placebo.

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3.1.4. Risk of bias between studies

Begg's method was applied to both outcomes, and no publication bias was found (P = 0.410). Figure 6 illustrates the evaluation of publication bias across studies employing these tests.

4. Discussion

The present study aims to assess the efficacy of omega-3 FA supplementation on markers of inflammation and endothelial function in CHD patients. The findings of this study demonstrated a remarkable decrease in circulating IL-6 levels after consuming an omega-3 supplement, suggesting that these fatty acids may have an anti-inflammatory role when it comes to CHD. Omega-3 supplement was found to significantly reduce hs-CRP, another inflam-

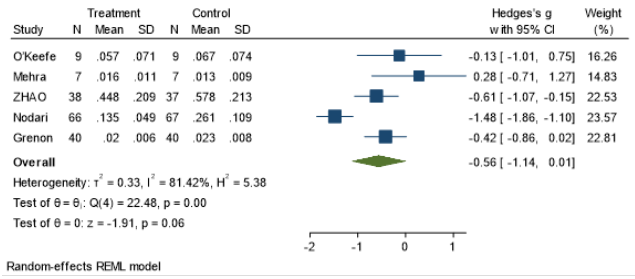

Fig. 4. Forest plots of the effect of omega-3 FA supplementation on TNF-α in CHD across the included studies are presented, with 95% CI calculated based on a random model. In the graphical representation, each square symbolizes the effect estimate from each study, with squares greater than the 95% confidence interval. The weights given to each study in the meta-analysis are reflected in the size of the squares. The total estimate is shown by a diamond.

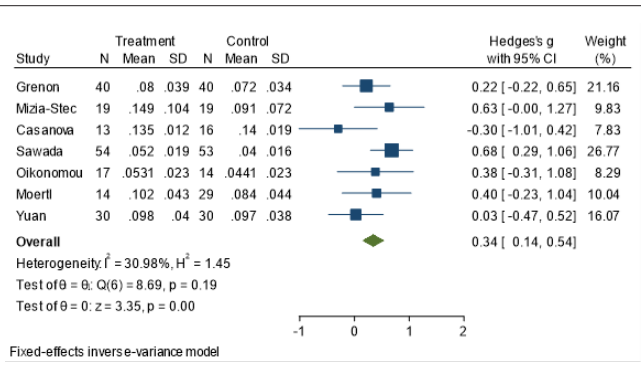

Fig. 5. Forest plots of the effect of Omega-3 FA supplementation on FMD in CHD across the included studies are presented, with 95% CI calculated based on a fix-effect model. In the graphical representation, each square symbolizes the effect estimate from each study, with squares greater than the 95% confidence interval. The weights given to each study in the meta-analysis are reflected in the size of the squares. The total estimate is shown by a diamond.

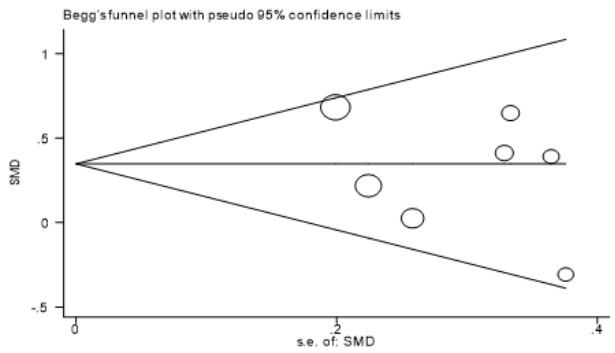

Fig. 6. Publication bias test using Begg's funnel plot test.

matory biomarker, which gives additional evidence to the anti-inflammatory characteristics of these FAs in the treatment of CHD. These results are consistent with Calder et al. study (2015) demonstrating the Omega-3 FAs' capacity to reduce inflammatory pathways by modulating cytokine production and immune cell function [30].

Additionally, the study investigated how omega-3 FAs affected CHD patients' TNF-α levels. Supplementing with omega-3 is associated with a considerable reduction in circulating TNF-α levels, which is in line with the findings related to IL-6 and hsCRP. The findings decrease in TNF-α levels corroborate the broad of omega-3 FAs anti-inflammatory impacts, further underscoring their potential therapeutic utility in CHD management [31].

In addition, endothelial dysfunction represents a crucial aspect of the pathogenesis of CHD. People are more vulnerable to cardiovascular events due to endothelial dysfunction, which also increases arterial permeability, impairs vasodilation, and promotes a prothrombotic state. An assessment of FMD, a surrogate marker of endothelial function, revealed a remarkable improvement after omega-3 supplementation. Enhanced FMD reflects improved endothelial-dependent vasodilation and vascular health, suggesting a beneficial effect of omega-3 FAs on endothelial function in CHD patients [32].

A meta-analysis study conducted by Xin et al. (2012) inconsistent with our results reported that supplementing with fish oil significantly decreased circulation levels of IL-6 and TNF-α, but had no effect on vascular cell adhesion molecular 1, soluble intracellular adhesion molecular 1, or hs-CRP.

Yan et al. (2022) [33] conducted a review study to assess the effectiveness and safety of various supplements containing omega-3 FAs. The findings showed that the omega-3 FA group had a lower incidence of myocardial infarction, main cardiovascular events, and cardiovascular death when compared to the control group. Omega-3 FAs supplementation substantially improves endothelial function without influencing endothelium-independent dilation, according to Wang et al. (2012) findings[34].

In a meta-analysis conducted by Natto et al. (2019) [35], the effects of omega-3 fatty acids on inflammatory biomarkers and fasting blood glucose levels in individuals with diabetes and cardiovascular disease (CVD) were assessed. The results suggest a potential association between omega-3 fatty acids and reduced inflammatory biomarkers in patients with diabetes and CVD [35]. Also, there are other reports [36,37].

Our study like any study has some limitations. The presence of significant heterogeneity among studies for certain outcomes underscores the need for a cautious interpretation of the pooled results. Variability in study design, patient characteristics, dosage regimens, and duration of supplementation may contribute to this heterogeneity. Additionally, while efforts were made to minimize bias through rigorous selection criteria and statistical analyses, the potential for residual confounding cannot be entirely excluded.

5. Conclusion

To sum up, this study presents convincing evidence of the potential therapeutic benefit of omega 3 FA supplementation in reducing inflammation and enhancing endothelial function in CHD patients. These findings highlight the need for more studies to clarify the best dosing methods and long-term impacts on clinical outcomes, which will have a significant impact on the management of CHD.

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Conflict of Interests
The author has no conflicts with any step of the article preparation.

Consent for publications
The author read and approved the final manuscript for publication.

Ethics approval and consent to participate
No human or animals were used in the present research.

Informed Consent
The authors declare not used any patients in this research.

Authors' contributions
The author did all the works in this Metha- analysis study.

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