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The effect of omega-3 fatty acids and vitamin e supplementation on lipid profiles and inflammatory markers in hemodialysis patients: A systematic review of current literature

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ABSTRAK

Latar Belakang: *Kebutuhan terapi hemodialisis (HD) masih terus berkembang. Di Indonesia, HD mewakili 82% dari pelayanan cuci darah di Puskesmas Indonesia. Namun, HD menyebabkan peningkatan penanda inflamasi serta perubahan profil lipid. Kombinasi vitamin E dan asam lemak omega-3 dapat membantu mengurangi indikator inflamasi dan meningkatkan profil lipid.*
Tujuan: *Penelitian ini bertujuan untuk mengetahui pengaruh co-suplementasi vitamin E dan omega-3 terhadap profil lipid dan indikator inflamasi.*
Metode: *Penelitian ini dilakukan di PubMed dan Google Scholar untuk mencari artikel-artikel secara sistematis, Kriteria inklusi yang digunakan adalah artikel bahasa Inggris dengan uji coba terkontrol acak (RCT) dan uji coba terkontrol (CT) yang menyelidiki efek vitamin E dan omega-3 pada profil lipid dan penanda inflamasi pasien hemodialisis. Semua artikel harus diterbitkan antara September 2013 - September 2022. AM dan AA melakukan seluruh proses penelitian sebagai reviewer dan seluruh ketidaksetujuan diselesaikan bersama NH sebagai penulis ketiga.*
Hasil: *1020 studi diidentifikasi dari database dan 12 artikel terpilih berdasarkan kriteria inklusi. Asam lemak omega-3 meningkatkan profil lipid, seperti kolesterol, LDL, HDL, dan trigliserida. Namun, studi ini hanya menemukan satu penelitian tentang efek vitamin E pada profil lipid. Asam lemak Omega-3 dan suplementasi vitamin E tidak memiliki efek signifikan pada penanda inflamasi, tetapi dampak suplementasi vitamin E pada tingkat IL-6 telah dilaporkan.*
Kesimpulan: *Co-suplementasi Omega-3 dan vitamin E berpengaruh pada penurunan level indikator inflamasi dan profil lipid pasien hemodialisis. Kami merekomendasikan bahwa studi berikutnya harus berfokus pada penelitian uji klinis mengenai pengaruh suplementasi kombinasi ini terhadap indikator inflamasi dan profil lipid pasien hemodialisis.*

KATA KUNCI: *hemodialisis, indikator inflamasi, omega-3, profil lipid, vitamin E*

ABSTRACT

Background: *Hemodialysis therapy (HD) demands is still growing. In Indonesia, HD represents 82% of dialysis services in Indonesian health centers. However, HD causes an increase in inflammatory markers as well as lipid profile changes. The combination of vitamin E and omega-3 fatty acids can assist to decrease inflammatory indicators and enhance lipid profiles.*
Objectives*: This study aims to investigate the effect of co-supplementation of vitamin E and omega-3 on lipid profiles and indicators of inflammation.*
Methods: *This study was conducted on PubMed and Google Scholar to search articles systematically. The inclusion criteria used were English articles of randomized controlled trials (RCTs) and controlled trials (CT) that investigated the effects of vitamin E and omega-3 on lipid*

profiles and inflammatory markers of hemodialysis patients. All articles must be published between September 2013 - September 2022. AM and AA conducted the entire research process as reviewers and all disagreements were finalized with NH as a third author.
Results: *1020 studies were identified from databases. Afterwards, this study included 12 articles based on the inclusion criteria. Omega-3 fatty acids improve lipid profiles, such as cholesterol, LDL, HDL, and triglyceride. While we only found a single study about the effect of vitamin E on lipid profile. Furthermore, omega-3 fatty acids and vitamin E supplementation have no significant effect on inflammatory markers, but the impact of vitamin E supplementation on IL-6 levels was reported.*
Conclusions: *Co-supplementation of omega-3 and vitamin E decrease levels of inflammatory indicators and lipid profiles in hemodialysis patients. We recommend that future studies should focus on clinical trials to investigate the effect of this co-supplementation on lipid profiles and inflammatory markers of hemodialysis patients.*

KEYWORD: *hemodialysis, inflammatory markers, lipid profiles, omega-3, vitamin E*

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INTRODUCTION

Recently, renal replacement treatment demand grows significantly (1). Despite the transplantation technology is quite advanced, 30-50% of patients who require renal replacement therapy typically consider hemodialysis (HD) as an alternative (2). In addition, HD represents 82% of dialysis services in Indonesian health centers (3). However, HD leads to several complications caused by the inflammatory process (4,5). This condition elevates proinflammatory cytokines which are linked to poor prognosis in HD patients (6). High-sensitivity C-reactive protein (hs-CRP), Interleukin-6 (IL-6), Interleukin-10 (IL-10), and tumor necrosis factor-alpha (TNF-α), were used to measure inflammation in HD patients (7). Also, routine HD affects the lipid profile, inducing dyslipidemia, as well as its implications potentially worsening renal diseases (8). A retrospective study conducted on 12,000 participants found that dyslipidemia causes an increase in kidney dysfunction (9). In patients with chronic kidney disease, 30-50% have a rise in inflammatory markers, including CRP and IL-6, with hemodialysis treatment being one of the causes (10).

Omega-3 has many beneficial effects on the human body, especially in reducing inflammation in HD patients (11). docosahexaenoic acid (DHA) have been Eicosapentaenoic acid (EPA) and proven to reduce the nuclear factor-kappaB (NF-kB) signaling pathway by blocking IkB phosphorylation and decreasing inflammatory-related genes expression. Furthermore, these improve the lipid profile, such as decreasing triglyceride (TG), low-density lipoprotein (LDL), and increasing high-density lipoprotein HDL (12). On the other hand, vitamin E has anti-inflammatory and antioxidant activities (13). Vitamin E has been shown to reduce inflammatory markers such as C-reactive protein (CRP), (IL-6) and TNF-α in macrophages. In addition, vitamin E also helps to improve lipid profiles and prevent other complications of diseases (14).

Antioxidants, such as vitamin E, play an important role in the oxidative stress caused by increasing omega-3 fatty acids oxidation sensitivity (13). However, both combinations allegedly are more effective than individual supplements and increase circulatory levels (15,16). Through decreased inflammation, oxidative stress, and inhibition of proinflammatory cytokines and NF-kB protein expression, omega-3 fatty acid and vitamin E intake may improve nutritional status and metabolic profiles (17). We investigate the effect of co-supplementing vitamin E and omega-3 fatty acids affected hemodialysis lipid

profiles and inflammatory indicators and carried out this study.

MATERIALS AND METHODS

Data search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines were used to conduct this systematic review (18). This study was performed on PubMed and Google Scholar to systematically search for relevant studies which were published from September 2013 to September 2022. We also conducted a manual search based on the reference lists in the included articles to seek out possible literature. The PICO (population, intervention, comparison, and outcome) rules were used in this study, including (1) P= chronic kidney disease patient with hemodialysis intervention for at least 3 months, (2) I= vitamin E or Omega-3 capsules, (3) C= replacement capsules as placebo, (4) O= lipid profile, such as total cholesterol, triglyceride, LDL, and HDL; Inflammatory markers, such as CRP, IL-6, IL-10, and TNF-alpha. The keywords were initially established, including: "hemodialysis patient", "vitamin E", "omega-3 fatty acid", "lipid profile", and "inflammatory markers". Furthermore, we included certain phrases based on MeSH terms and arranged them by using Boolean Operators, such as “AND” and “OR”. The search was restricted to human participants only, and without language restrictions. The entire research process was carried out by 2 reviewers (AM and AA) and all disagreements were resolved by discussing with the third author (NH).

Eligibility criteria

This study's criteria for inclusion were as follows: (1) studies with randomized control trials (RCTs) or control trials (CTs); (2) English articles; (3) adult hemodialysis patients; (4) having undergone HD treatment for at least 3 months; (5) the measured outcomes were comparing lipid profiles or inflammatory markers after vitamin E or omega-3 supplementation. While irrelevant titles and abstracts, irretrievable full-text, review papers, and conference abstracts were employed as exclusion criteria in this study.

Data extraction and quality assessment

Data extracted from the involved studies, including (1) author and year of publication; (2) location; (3) study design; (4) total number and age range of included patients; (5) at least received 3 months HD intervention; (6) capsules of vitamin E or omega-3 supplementation; (7) lipid profile outcomes, such as TG, total cholesterol (TC), LDL, and HDL; and (8) inflammatory marker outcomes, such as CRP, IL-6, IL-10, and TNF-α. A quality evaluation was performed to identify suitable papers for this study using the Joanna Briggs Institute (JBI) critical appraisal checklist (19,20). Studies with 50% or higher will be considered. Eligibility based on the inclusion criteria and data extraction were done by two authors as equal first authors (AM and AA). These are carried out to evaluate the methodological quality of the study included by providing a value of "YES," "NO," "NOT CLEAR," or "NOT ANSWER." Only those "YES" responses are assigned a score of one, while all other responses have a value of zero. Methodological quality assessment was only carried out by one author (AM) to avoid differences in measurement.

RESULTS AND DISCUSSIONS

Figure 1 represents the flow of search results using PubMed and Google Scholar. This study identified 1020 articles from PubMed (22 articles) and Google Scholar (998 articles). However, according to duplication, 25 articles were eliminated before the screening process. Thereafter, 995 items were screened by title, and 877 were excluded. Furthermore, 80 articles were identified to be removed after being reviewed based on the abstracts. As a result of these two elimination procedures, 38 articles were identified to perform the retrieval process. Assessment of study eligibility was performed on a full-text basis for several reasons, such as; excluding five articles with illegible study designs, ten articles with unsuitable participant characteristics, six articles with illegible outcomes which were not correlated with our

study, and other reasons related to the lack of full-text studies. Afterwards, 12 articles which have been included were evaluated based on the JBI Score critical appraisal, and all studies were eligible to be included.

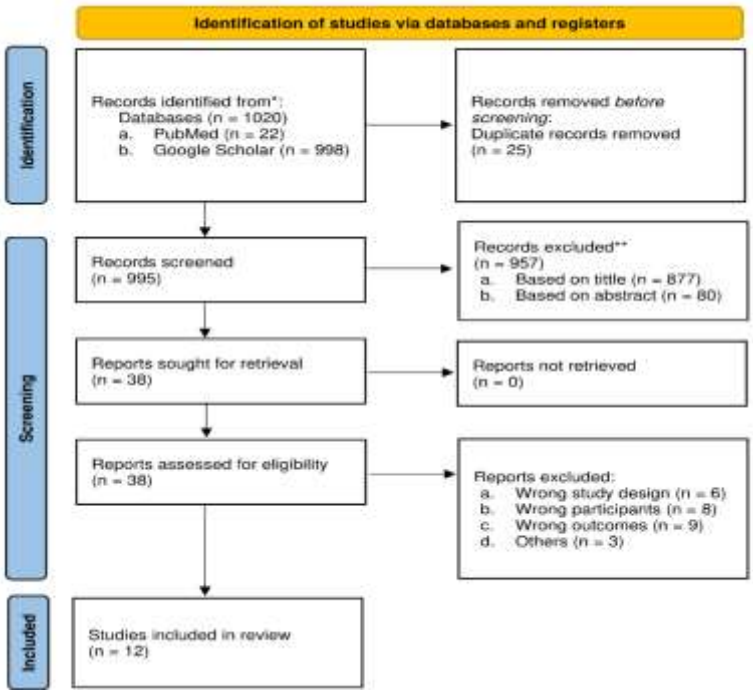

Figure 1. PRISMA 2020 Flow Chart of This Study

The results are presented in **Table 1**. This study investigated the role of vitamin E and omega-3 administration on HD patients' lipid profiles and inflammatory parameters. Five studies stated that omega-3 supplementation reduced total cholesterol TC levels, but only two studies which were found significant differences in TC levels after omega-3 supplementation. Omega-3 supplementation caused a significant difference in serum TC levels (15,21,22). Administration of 1800 mg of omega-3 reduced cholesterol levels significantly (22). In addition, ten weeks of 1000 mg omega-3 supplementation can be also decreased TC levels (21). However, Mattos et al.(23) stated the opposite, that supplementation of two capsules of fish oil containing 840 mg EPA and 440 mg DHA for 12 weeks did not cause a significant difference in TC levels (23). Another study showed an insignificant difference in TC (24). However, omega-3 supplementation did not contribute to any significant improvement in TG levels. Four articles analyzed in this study stated that omega-3 supplementation at different durations and doses was not able to significantly reduce TG levels (15,21,23–25).

Six of the twelve papers we identified assessed blood LDL-C levels before and after omega-3 administration. However, only one study found a significant difference in LDL-C levels after 1800 mg daily omega-3 supplementation for four months (22). However, there was not found LDL-C change significantly in a 12-week study with a greater dosage (23). This was further confirmed in different investigations with varying dosages and dosing duration (15,21,22,25,26). Serum HDL-C levels were evaluated before and after omega-3 administration in seven of the 12 papers we found. Omega-3 capsules containing 180 mg EPA and 120 mg DHA were administered for 4 months (22) and six months (24,25) increasing HDL-C levels significantly. In addition, Bashardoost et al. (26) showed oral administration of 800 mg EPA+900 mg DHA

capsules for three months elevated HDL-C levels (26). However, different studies stated that omega-3 supplementation did not affect HDL-C levels (15,21,23).

Five papers investigated the vitamin E supplementation effect on lipid profile and inflammatory markers. Nevertheless, we only found a study which was assessed the role of vitamin E in lipid profile improvement (15), while the other study evaluate the vitamin E supplementation effect on inflammatory markers (27–30). However, Asemi et al. (31) found that 12 weeks of supplementation of vitamin E 400 IU did not lead to a significant difference between before and after supplementation (15).

During this investigation, we extracted three articles which were evaluated CRP improvement after omega-3 administration (11,22,25). However, we found a particular study which was showed a significant difference after supplementation (11). Four capsules of omega-3 supplementation decrease CRP levels (11), however other studies showed the CRP level significant change is none (22,25). We found four articles which were evaluated CRP levels after vitamin E capsules administration in HD patients. One of them reported a significant difference in serum CRP levels before and after 400 IU vitamin E supplementation for eight weeks (29). Nevertheless, in similar dosages and duration of supplementation, there were no significant differences in serum CRP levels (27). Furthermore, 200 IU of vitamin E administration for 10 weeks did not affect lowered hs-CRP levels significantly (30).

Among the 12 articles we identified, a single study reported the effect of omega-3 capsules on levels of IL-6 as a measure of inflammation. The delivery of four capsules of omega-3, 360 mg EPA and 240 DHA, substantially reduced levels of IL-6 and TNF-α. Furthermore, IL-10 levels were examined after supplementation in this study, although there was no significant variation in IL-10 levels after supplementation (11). Salehi et al. found there was no significant difference in TNF- levels after omega-3 supplementation (25). Moreover, the impact of vitamin E supplementation on IL-6 levels was reported (27,29,30), and one of them showed that 400 IU of vitamin E for two months decreased IL-6 levels significantly (27). Jafari et al.(32) showed that there was no significant difference between TNF-α levels after vitamin E supplementation (29).

The combination of 1250 mg/day of omega-3 and 400 IU of vitamin E supplementation for 12 weeks has not shown any significant changes in TC levels. TG. LDL-C and HDL-C (15). In addition, Zakaria et al. (28) also reported the combination of fish oil containing 1053 omega-3 and wheat germs oil containing 0.765 vitamin E for 4 months also did not show a significant difference in CRP (28).

Omega-3 fatty acids can modify cell membrane structure and function, as well as lipid mediator synthesis (such as eicosanoids) and fatty acid gene expression, and lead to improvements in the lipid profile (33). In particular, omega-3 fatty acids influence the function of peroxisome proliferator-activated receptors and sterol regulatory binding proteins, which are both involved in lipid homeostasis (34). The direct inhibition of TG synthesis and the reduction of very low-density lipoprotein (VLDL) assembly and secretion are the primary mechanisms of omega-3 fatty acids in improving the lipid profile (35). On the other hand, TG was lowered by omega-3 levels by increasing fatty acid oxidation, which results in fewer fatty acids available for TG synthesis. Finally, omega-3 fatty acids improve TG clearance rates by increasing plasma lipolytic activity. Most likely due to a reduced substrate for lipoprotein lipase action, omega-3 fatty acids also reduce the hepatic synthesis of VLDL-ApoB while increasing the conversion rate of VLDL to LDL (36).

Table 1. Characteristics of the effect of vitamin e and omega-3 supplementation studies on lipid profiles and inflammatory markers of patients on hemodialysis treatment

Authors and Year	Study Design	n	Participant	Intervention	Placebo	Duration	Outcomes	Results	JBI Score
Mattos et al., 2017 (23)	RCTs	88	Aged ≥ 18 years and ≥6 months HD	Two capsules of fish oil, n-3 PUFA (EPA: 840 mg); (DHA: 440 mg)	Soybean oil	12 weeks	TC, TG, HDL-c, and LDL-c levels	There was no significant difference after fish oil supplementation	
Valle Flores et al., 2020 (11)	RCTs	102	Aged ≥ 18 years and ≥ 6 months HD	Four capsules of Omega-3 (360 mg of EPA; 240 mg DHA)	Not defined clearly	12 weeks	CRP, IL-6, IL-10, and TNF-α	A significant difference in all inflammatory markers after supplementation existed, except IL-10	
Gharekhani et al., 2016 (22)	RCTs	45	Adult patients who received HD treatment ≥ 3 months	6 soft-gel; capsules of 1800 mg of omega-3 fatty acids (180 mg of EPA and 120 mg of DHA)	Paraffin oils in soft-capsules	4 months	TC, LDL-C, HDL-C, and CRP	Significant differences existed on TC, HDL-C, and LDL-, except CRP	
Moeinzadeh et al., 2016 (24)	RCTs	52	Adult patients who received HD treatment ≥ 3 months	Omega-3 capsules 1 gram (180 mg of EPA and 120 mg of DHA)	Similar capsules	6 months	HDL-C, LDL-C, TG, TC	A significant statistic existed on HDL-C levels. However, other markers were not significant.	
Omrani et al., 2015 (21)	CTs	60	Adult patients who received ≥ 6 months	Omega-3 capsules 1000 mg daily (80 mg of EPA; 120 mg DHA)	Vitamin E capsules with a similar appearance	10 weeks	TC, TG, LDL-C, HDL-C	Omega-3 supplementation only lowered serum total cholesterol levels significantly	
Bashardost et al., 2019 (26)	CTs	57	Adult HD patients	MAX omega-3 capsules (900 mg DHA and 800 mg EPA)	Not clearly defined	3 months	LDL-C, HDL-C	There was no significant difference in LDL level, but on HDL level was significant	
Salehi et al., 2017 (25)	RCTs	54	Aged ≥ 18 years and received ≥ 3 months HD treatment	3 capsules of 1 gram omega-3 (180 mg EPA; DHA 120 mg)	Similar capsules	6 months	LDL, TG, cholesterol, HDL, CRP, and TNF-α	Omega-3 supplementation had no significant effect on these parameters, except HDL level	
Asemi et al., 2016 (15)	RCTs	120	Aged 18-80 years and received ≥ 1 year HD treatment	a. Administration of 1250 mg/day omega-3 (600 mg EPA and 300 mg DHA) and placebo b. 400 IU/day of vitamin E and placebo	Similar capsules	12 weeks	TG, TC, LDL-C, HDL-C	There is no statistically significant of vitamin E or omega-3 or both combination supplementation effect on these parameters	

Authors and Year	Study Design	n	Participant	Intervention	Placebo	Duration	Outcomes	Results	JBI Score
				C. Combination of 1250 mg omega-3 fatty acids/day and 400 IU/day vitamin E					
Pirhadi-Tavandashti et al., 2020 (30)	RCTs	49	Aged 20-60 years and received ≥ 3 months of HD treatment	Three times daily 200 IU alpha-tocopherol soft gels	Oral paraffin soft capsules	10 weeks	Hs-CRP and IL-6	There was no significant effect of vitamin E supplementation on hs-CRP and IL-6	
Jafari et al., 2020 (29)	RCTs		Received ≥ 3 months of HD treatment	Vitamin E soft gel (400 IU) daily	Paraffin oil	8 weeks	CRP, IL-6, TNF-α	Vitamin E reduced CRP levels, however, there were no significant effects on IL-6 and TNF-α level	
Ahmadi et al., 2015 (27)	RCTs	85	Aged 20-60 years and received ≥ 12 months of HD treatment	vitamin E (400 IU)	Not defined clearly	2 months	CRP and IL-6	Vitamin E supplementation reduces IL-6, however, there were no significant effects on the CRP level	
Zakaria et al., 2017 (28)	RCTs	46	Aged ≥ 20 years and ongoing regular HD treatment ≥ 6 months	Daily 3000 mg of fish oils (1053 mg omega-3 fatty acids) and 300 mg of wheat germ oils (0.765 mg vitamin E)	Corresponding capsules	4 months	CRP	There is no statistically significant effect on the CRP level	

Abbreviation

C-reactive protein (CRP), Control trials (CTs), Docosahexaenoic acid (DHA), Eicosapentaenoic acid (EPA), Hemodialysis (HD), High-density lipoprotein (HDL), High-density lipoprotein-cholesterol (HDL-C), Interleukin-6 (IL-6), Interleukin-10 (IL-10), Low-density lipoprotein (LDL), Low-density lipoprotein-cholesterol (LDL-C), Polyunsaturated fatty acid (PUFA), Randomized control trials (RCTs), Triglyceride (TG), Total cholesterol (TC), Tumor necrosis factor-alpha (TNF-α)

However, some studies have found that omega-3 fatty acids did not affect lipid profiles. The effect of omega-3 fatty acids at normal doses is unknown, as is the long-term effect of omega-3 supplementation (37).

The protective action of omega-3 fatty acids against the damaging effects of TNF-α is commonly linked to reduced inflammation (38). However, there is limited information available about fatty acid levels in dialysis patients. A study by Bowden et al. (39) has discovered that consuming 960 mg/d eicosapentaenoic acid and 600 mg/d DHA can reduce CRP levels. Low-dose omega-3 fatty acids, on the other hand, did not affect plasma hs-CRP levels (39). The response to omega-3 fatty acid supplementation varies due to differences in the fatty acid pool assessed, subject population variability, and genetic differences (40).

Although vitamin E may influence lipoprotein oxidation, there is no evidence that it influences serum lipid levels. According to Daud et al. (14), giving vitamin E may not have produced beneficial results for blood lipids because it lasted less time, used less dose, and had smaller samples (14). A recent study in which healthy older adults were given vitamin E for a longer period (six months) discovered a significant improvement in their lipid profiles (increased HDLC and improved TC/HDLC ratios) (41), supporting the idea that the effects of vitamin E on blood lipids may vary over time and may be influenced by a subject's clinical status (14).

Vitamin E can prevent lipid peroxidation by scavenging free radicals due to its antioxidant activity (42). Both the antioxidant and non-antioxidant effects of vitamin E can control inflammation. Vitamin E increases the activity of activator protein 1 (AP1), which in turn can dephosphorylate PKC, inhibit the production of reactive oxygen species by monocytes, and reduce inflammation (30). Furthermore, the anti-inflammatory effects of vitamin E were mediated by the inhibition of the enzymes cyclooxygenase (COX) and arachidonate 5-lipoxygenase (43). Some studies have shown vitamin E supplementation reduced inflammatory cytokines, such as TNF-α and IL-6. Its effect as an antioxidant prevented translocation of NF-κB proteins to the nucleus that reduced IL-6 mRNA and protein in different tissues in response to inflammation. The decrease in inflammatory cytokines could also be attributed to an increase in anti-inflammatory cytokines, specifically interleukin-10 (IL-10) and a reduction in IκB kinase-β (IKKβ) (44).

Although some articles produced positive results, there are some limitations. In the primary, regardless of whether clear inclusion and exclusion criteria were established, significant differences in study design, intervention, and outcome measurement remained. Furthermore, our study can only look at a small number of journals that have published studies on the impact of vitamin E and omega-3 fatty acid co-supplementation on lipid profiles and inflammatory markers in hemodialysis patients. Third, the minimal doses and duration of omega-3 fatty acids and vitamin E to have an impact on lipid profiles and inflammatory markers remain unclear. These aspects may affect our results. However, according to a study by Jafari et al., vitamin E supplementation had a positive correlation with improving the quality of life in hemodialysis patients, particularly in mental components (45).

CONCLUSIONS AND RECOMMENDATIONS

Conclusion

Omega-3 and vitamin E co-supplementation have the potential to ameliorate inflammatory markers and lipid profiles in hemodialysis patients. Omega-3 and vitamin E suppress inflammatory markers levels, such as CRP, IL-6, and TNF-α, and improve lipid profiles, such as TG, TC, LDL, and HDL. However, there is still no significant effect of omega-3 on IL-10. In addition, research on the effect of vitamin E on IL-10 carried out in hemodialysis patients has also not been found.

Recommendations

The following study should be the focus of the future clinical trial. The dosage,

route, timing, and duration of vitamin E and omega-3 co-supplementation for lipid-altering action and inflammatory markers need to be better elucidated and accurate. Although co-supplementation of omega-3 and vitamin E was previously thought to be safe and feasible, more research is needed to determine the long-term effects of supplementation. Finally, future studies should focus on the effect of omega-3 fatty acids and vitamin E on reducing inflammation in dialysis patients.

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