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Effect on Vitamin D supplements and Fatty Acids in management of cardiovascular diseases

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ABSTRACT

Introduction: n-3 polyunsaturated fatty acids (PUFA) and vitamin D exclusively and have been the focus of numerous research regarding their possible significance in lowering cardiovascular risk. Numerous physiological processes, including signal transduction, ion channel kinetics, and protein and membrane trafficking are modulated in part by lipid microdomains. The inclusion of n-3 PUFA modifies the physical characteristics of cellular and organelle membrane structures and affects the positioning, functioning, and signaling of membrane-associated proteins.

Aims and Objectives: To analyze the effect of vitamin D supplements and fatty acids on the management of cardiovascular diseases.

Methods: This is a prospective study which was conducted on 80 patients for whom cardiovascular abnormalities were considered and their parameters were determined before administration of n3 fatty acids and Vitamin D3. After 6 months course of drugs containing n3 fatty acids and Vitamin D3, the cardiovascular abnormalities including mortality were assessed for end outcome. The statistical analysis was conducted to determine the significance of the improvement.

Results: The study found that end assessment showed that ischemic stroke (p=0.032) and cardiovascular mortality (p=0.023) were significantly found to be less in the n-3 FAs group and vitamin - D group compared to the control group.

Conclusion: The study concluded that administration of n-3 FAs group and vitamin - D at a mentioned dosage for 6 months may lead to a statistically significant reduction in cardiovascular mortality and ischemic stroke as compared to healthy controls.

Keywords: *Vitamin D, fatty acids, polyunsaturated fatty acids, cardiovascular diseases*

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INTRODUCTION

Cardiovascular disease can be prevented and treated in a variety of ways. A growing part of the conservative management of cardiovascular disease involves food modification and supplements, in addition to pharmacological treatment and changes in lifestyle. There are literature which dealt with n-3 polyunsaturated fatty acids (PUFA) and vitamin D exclusively and have been the focus of numerous research regarding their possible significance in lowering cardiovascular risk [1,2]. Cardiac arrhythmias, heart failure, and coronary artery disease (CAD) may all be treated with n-3 PUFA. There are signs that they may be used in addition to the usual diabetes treatment and treatment of hypertriglyceridemia [3].

Widespread interest has been given to vitamin D because of its potential to reduce the risk of type 2 Diabetes and cardiovascular disease (CVD). According to a number of epidemiological studies, those with low blood levels of vitamin D are at increased risk of diseases of heart, strokes, high blood pressure, and diabetes. A blood 25-hydroxyvitamin D level of 20 ng/mL or higher (50 nmol/L) in conditions of moderate sun exposure is the recommended dietary allowance for vitamin D based on bone health for people aged 1 to 70 and 800 IU/d for those over 70 [4,5]. Interaction between Vitamin D, cardiovascular abnormalities and diabetes have been shown below in Figure 1.

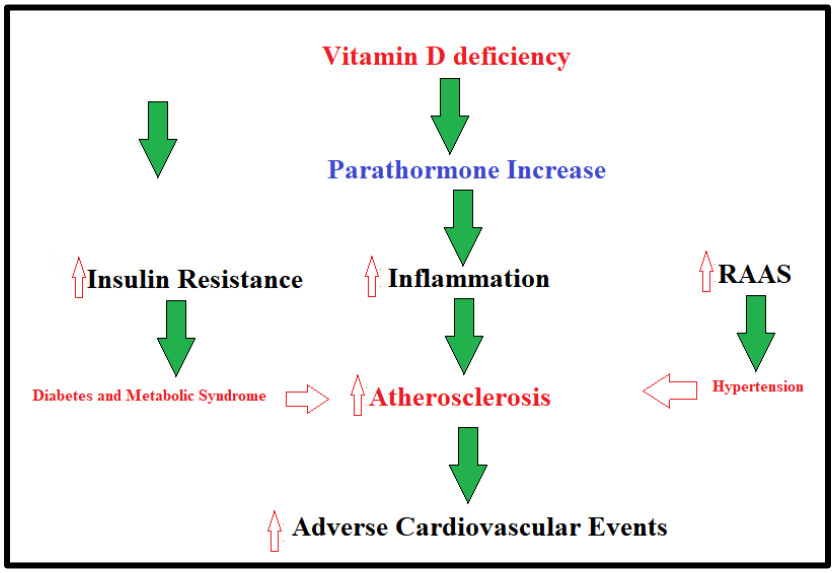

FIGURE 1: Interaction between Vitamin D, cardiovascular abnormalities and diabetes

One of the ongoing studies examining how marine omega-3 fatty acids and vitamin D contribute to the primary prevention of cancer and CVD is called VITAL. It is a randomized, double-blind, placebo-controlled clinical trial with an oversampling of blacks that is open to American men and women without cancer or CVD at baseline who are selected only based on age (men aged 50 and women aged 55) [6,14]. Testing the effects of vitamin D supplementation is crucial since black people have a higher risk of vitamin D insufficiency, as well as a higher risk of some malignancies (such as prostate cancer) and cardiovascular events (such as stroke), as well as mortality from CVD [7-9].

The action of n-3 PUFA on various important molecular pathways is the reason for the possible impact on cardiovascular risk factors. The lipid surroundings of membranes have a significant impact on cellular and organelle activities [10,11]. Numerous physiological processes, including signal transduction, ion channel kinetics, and protein and membrane trafficking are modulated in part by lipid microdomains [12]. The inclusion of n-3 PUFA modifies the physical characteristics of cellular and organelle membrane structures and affects the positioning, functioning, and signaling of membrane-associated proteins [13]. Potential antiarrhythmic and anti-inflammatory effects may be influenced by this. Omega-3 fatty acids may also have a

direct electrical effect on the myocardium, according to several clinical studies for arrhythmias and sudden cardiac death following ischemia [15,16].

Cardiovascular disease can be prevented and treated in a variety of ways. A growing part of the conservative management of cardiovascular disease involves food modification and supplements, in addition to pharmacological therapy and lifestyle changes. The focus of recent research has been on vitamin D and n-3 polyunsaturated fatty acids (PUFA) [23]. Numerous research have looked into their potential to lower cardiovascular risk. Heart failure, cardiac arrhythmias, and coronary artery disease (CAD) may all be treated with n-3 PUFA. There are signs that they can be used in addition to the usual treatment for diabetes and hypertriglyceridemia. In terms of cardiovascular outcomes, the findings of several clinical investigations are encouraging. For instance, the GISSI-P research demonstrated that daily omega-3 fatty acid (FA) supplementation, when combined with medical therapy, can lower cardiac and all-cause mortality in individuals with myocardial infarction [24].

In most tissues, the vitamin D receptor (VDR) is expressed. The secosteroid family of chemicals, which includes bioactive vitamin D, is known to play a role in the metabolism of calcium and bones. When exposed to sunshine, the human body can make vitamin D from 7-dehydrocholesterol, which constitutes the majority (80% to 90%) of this chemical in humans [23]. Hypertensive vascular disease, coronary artery disease, cardiac arrhythmias, peripheral vascular disease, lipid metabolism, and diabetes mellitus may all be treated or prevented by vitamin D. Experimental results generally support the idea that vitamin D has a preventive function in cardiovascular health, and growing epidemiologic research shows that hypovitaminosis D may be linked to a higher risk of cardiovascular events [25].

MATERIALS AND METHODS

Study design

This is a prospective study which was conducted on 80 patients who visited the outpatient department. The study was done from December, 2021 to December, 2022. The patients of cardiovascular abnormalities were considered and their parameters were determined. After a 6 months course of n3-FA (1g/d fish-oil capsule with 840 mg of n-3 FAs, including eicosapentaenoic acid, 460mg + docosahexaenoic acid 380mg) and Vitamin D3 (2000 IU/d), the parameters attributed to cardiovascular status.

To determine the advantages and disadvantages of supplemented marine n-3 FAs and vitamin D3 in the main prevention of cardiovascular disease and cancer amongst women and men, aged 50 and over, a randomized, double-blind, placebo-controlled experiment was conducted. The study was conducted on patients who came to the outpatient department of our hospital, 80 participants were included in the study and were grouped into two vitamin D and n3 fatty acids.

A 24-hour dietary questionnaire measured the intake of fish, milk products, and other foods; the baseline questionnaire collected information on clinical and lifestyle risk factors for cancer, CVD, and other disorders. Annual follow-up questionnaires evaluated endpoint incidence, risk factor updates, and therapy compliance and side effects. The National Death Index Plus and other sources were used to determine deaths, and participant-reported endpoints were confirmed or disconfirmed by medical record review using established standards by doctors who were blind to the therapy allocation. All willing participants' baseline blood samples were obtained during the run-in.

Inclusion and exclusion criteria

A past myocardial infarction (MI), coronary revascularization, transient ischemic attack, stroke, or cancer (apart from non-melanoma skin cancer) was not permitted for eligible individuals. They had to consent to stop using fish oil supplements and to set daily limits for calcium and vitamin D intake from all dietary supplements, including multivitamins, of no more than 800 IU and 1200 mg, respectively.

Kidney failure or dialysis, serious liver illness (cirrhosis), the use of blood thinners, a history of parathyroid problems or hypercalcemia, or other factors that would prevent participation were also safety exclusions.

Statistical Analysis

The study has used SPSS 25 and MS Excel for effective analysis. The continuous variables were expressed as mean ± standard deviation. The discrete variables were expressed as counts and its respective percentage. The statistical method employed for analyzing continuous variables was ANOVA while for discrete variables was chi-square. The level of significance was considered to be $\alpha = 0.05$.

Ethical approval

The patients were given a thorough explanation of the study by the authors. The patients' permissions have been gotten. The concerned hospital's ethical committee has accepted the study's methodology.

RESULTS

The total number of participants is 80 divided equally into two groups n-3 FAs and vitamin D (table 1). The number of males and females is equal. The mean age of participants is 67.5. The mean BMI is 28.3 in both the groups. The percentage of current smokers is high in test group (7.5%) compared to control (5%). The participants with treatment of hypertension (52.5), diabetes (17.5%), aspirin usage (50%), cholesterol lowering dose (40%) were high in test group.

TABLE 1: Baseline characteristics of participants

Baseline characteristics of patients	All participants	N-3 fatty acids and Vitamin D	Control
Total number	80	40	40
Females number (%)	40 (50)	20 (50)	21 (52.5)
Age, years, mean ± SD	67.5 ± 7.3	67.5 ± 7.3	67.5 ± 7.2
ethnicity/ race- number (%)			
Non-Hispanic White	57 (71.2)	30 (75)	28 (70)
African American	16 (20)	8 (20)	9 (22.5)
Hispanic (not African American)	3 (3.75)	3 (7.5)	2 (5)
Asian/ pacific islander	1 (1.25)	2 (5)	1 (1.25)
Native American	1 (1.25)	0	0
Other or unknown	2 (2.5)	2 (5)	1 (1.25)
Body mass index, kg/m2, mean ± SD	28.3 ± 5.5	28.3 ± 5.5	28.3 ± 5.6
Current smoking (%)	6 (7.5)	3 (7.5)	2 (5)
Hypertension treated with education-number (%)	40 (50)	21 (52.5)	20 (50)
Cholesterol-lowering medication, current use- number (%)	30 (37.5)	16 (40)	15 (37.5)
Diabetes- number (%)	10 (12.5)	7 (17.5)	6 (15)
Current regular aspirin use- number (%)	36 (45)	20 (50)	19 (47.5)

Table 2 shows that the participants are equally divided among N-3 FAs and control group. The end points in the table are cardiovascular diseases, and other vascular outcomes like ischemic stroke, all- cause mortality, and cancer mortality. The ischemic stroke (p=0.032) and cardiovascular mortality (p=0.023) are significantly less in the n-3 FAs group and vit-D group compared to the control group.

TABLE 2: Prognostic Outcome assessment of both the groups

End point	N-3 FAs and vit- D (n = 40)	Control group (n = 40)	P-value
Cardiovascular diseases			
Total myocardial infarction	12	15	0.73
Total stroke	18	17	1.05
Cardiovascular mortality	10	21	0.023
Coronary heart disease	12	11	0.751
Other vascular outcomes			
Ischemic stroke	10	22	0.032
Cancer mortality	13	12	0.96
All-cause mortality	17	16	0.854

The study has shown comparative mortality rates due to cardiovascular diseases in Figure 2. It shows schematic representation of mortality rates. The group which had n3-FA and vitamin D had much lesser mortality rate due to cardiovascular diseases while coronary heart disease did not respond in "n3-FA and vitamin D" group.

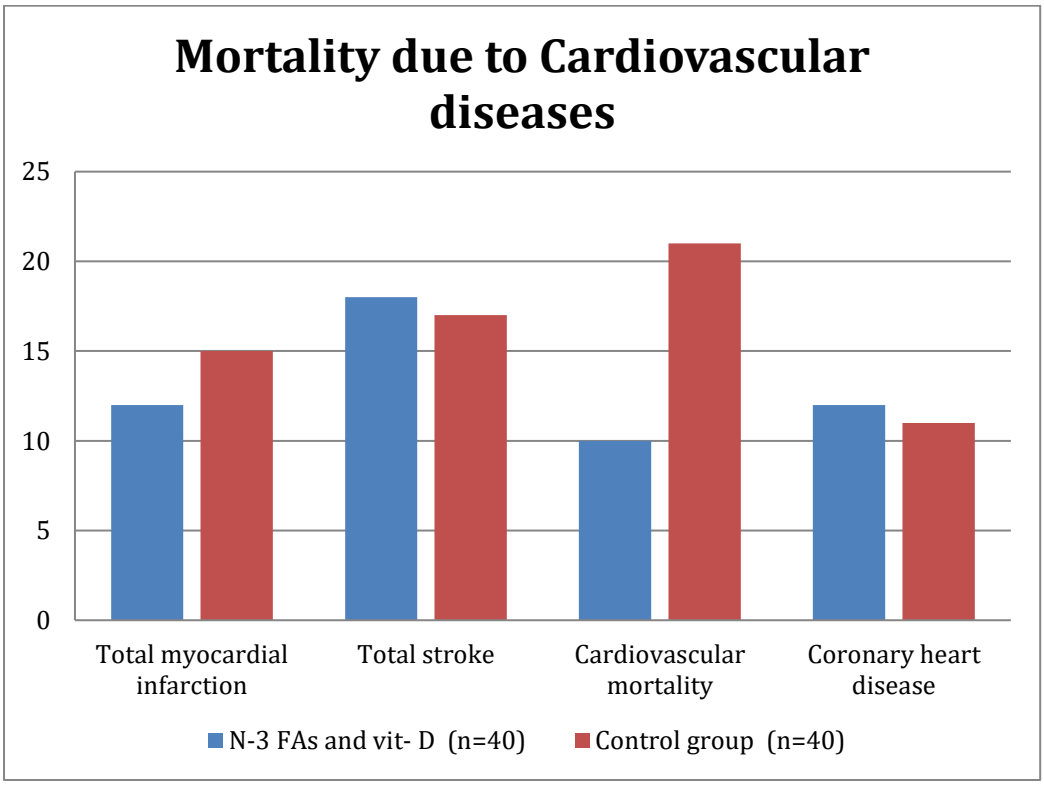

FIGURE 2: Mortality Rate due to cardiovascular diseases in this study

In Figure 3, it can be found that ischemic stroke is much more in the "n3-FA and Vitamin D" group than the control group, while cancer mortality and all-cause mortality have no significance in the "n3-FA and Vitamin D" group as compared to the control group.

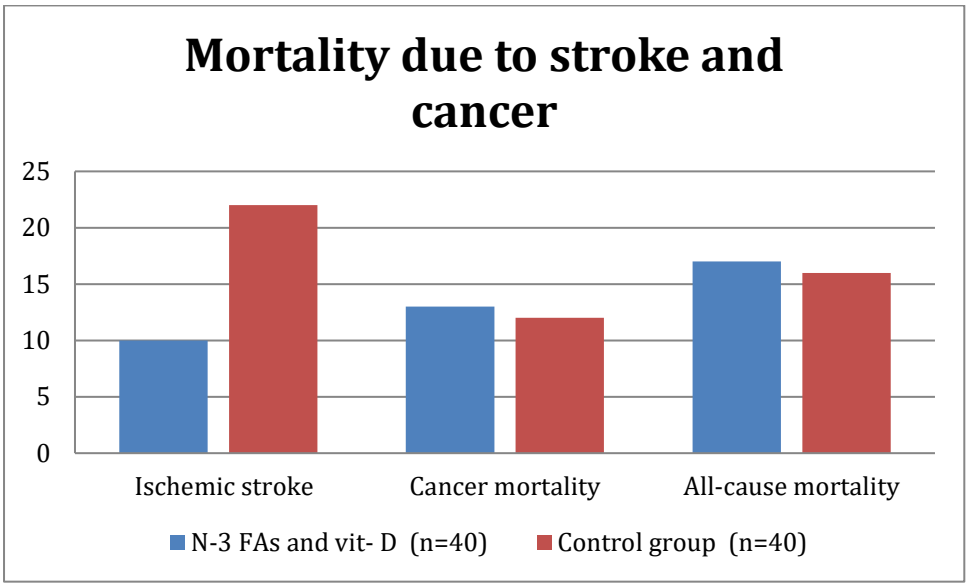

FIGURE 3: Mortality Rate due to stroke and cancer related diseases in this study

DISCUSSION

There is conflicting research regarding the health advantages of diets high in n-3 polyunsaturated fatty acids (PUFA), vitamin E (alpha-tocopherol), and its pharmaceutical equivalents. We looked into how these dietary supplements affected myocardial infarction patients. Treatment with n-3 PUFA significantly reduced the risk of the main outcome but not vitamin E. A reduction in the risk of death and cardiovascular death was responsible for the benefit. The combined therapy had similar results to n-3 PUFA for both the primary endpoint and fatal events [17].

Beyond issues with bone and calcium metabolism, observational studies firmly link vitamin D insufficiency to a number of cardiovascular illnesses. Numerous pathways of vitamin D have the potential to impact cardiovascular health. Vitamin D replacement therapy may be helpful because vitamin D insufficiency is frequently present. The few trials that have been conducted to date examining vitamin D supplementation have not consistently demonstrated effectiveness. It's likely that inadequate vitamin D supplementation levels or other unidentified factors led to the lack of benefit in these studies. However, the expanding amount of observational data and recurrent discoveries of relatively high rates of low vitamin D serum levels call for more, carefully planned research to examine the connection between vitamin D and cardiovascular health. In conclusion, vitamin D is now understood to be crucial for cardiovascular health, and a lack of it may increase the chance of developing a number of cardiovascular disease processes [18,19].

Docosahexaenoic acid and eicosapentaenoic acid, which are found in fish oils, and alpha-linolenic acid, which is found in flaxseed oil, are examples of common omega 3 polyunsaturated fatty acids (n-3 PUFAs). Studies on epidemiology revealed that n-3 PUFAs are good for cardiovascular health. Intervention studies proved that n-3 PUFA consumption was advantageous for both primary and secondary cardiovascular disease prevention [19,22]. The cardioprotective effects of n-3 PUFA are thought to be the result of a synergy between numerous, complex mechanisms, including anti-inflammation, pro-resolving lipid mediators, reduction of triglycerides, modulation of cardiac ion channels, influence on membrane microdomains and downstream cell signaling pathways, and antithrombotic and antiarrhythmic effects, according to evidence from cellular and molecular research studies. The expression of genes involved in fatty acid (FA) synthesis is downregulated while that of genes involved in FA oxidation is upregulated by n-3 PUFAs, which also decrease inflammatory signaling pathways [20,21].

The widespread distribution of VDR and tissue 25(OH)D-1-hydroxylase sheds light on a number of pathobiologic mechanisms by which hypovitaminosis D may influence vascular health. Increased blood pressure, serum angiotensin, and tissues renin are all characteristics of the VDR knockout mouse, an animal model simulating vitamin D deficiency. Through a vitamin D response element found in the renin gene, vitamin D analogues directly decrease the expression of the renin gene in in vitro investigations [20]. Analogs of vitamin D have been demonstrated to stimulate the actions of Th-2 lymphocytes, resulting in a decrease in matrix metalloproteinase and a reduction in plaque development and instability, while inhibiting the production of many proinflammatory Th-1 cytokines, such as IL-2 and IFN- [22]. Additionally, it has been demonstrated to have immunosuppressive effects that reduce lymphocyte proliferation and cytokine production, both of which have been linked to atherogenesis. The downregulation of plasminogen activator inhibitor 1 in human aortic smooth muscle cells by VDR agonists has also been seen, but not in endothelial cells. Additionally, it appears that vitamin D inhibits vascular calcification in a dose-dependent manner [23].

A significant cardiovascular risk factor has been identified as chronic kidney disease (CKD). According to Agarwal et al., vitamin D has a direct vascular effect since it reduced proteinuria in 51% of the 57 CKD patients who got an activated vitamin D analogue (paricalcitol) compared to only 25% of the 61 research participants who received a placebo (P = 0.004). According to several observational studies, patients with CKD and low serum 25(OH)D levels are more likely to pass away. In accordance with other studies, individuals with CKD who receive treatment with activated vitamin D have lower all-cause and cardiovascular mortality [25].

Numerous putative mechanisms have been proposed to link vitamin D insufficiency to a broad range of cardiovascular disorders. A significant risk factor for cardiovascular disease is essential hypertension. Multiple routes seem to link vitamin D and blood pressure regulation, and it is inversely correlated with serum renin activity. Clinical research has revealed an inverse relationship between vitamin D levels and systolic and diastolic blood pressure as well as vascular resistance [26]. A different study, however, found no correlation between vitamin D levels in newly diagnosed hypertension patients and their matched controls. The link among vitamin D levels and peripheral vascular disease was also seen in the NHANES III investigation. The possible pathways of elevated CV risk from vitamin D insufficiency are depicted here. A lack of vitamin D can increase the risk of hypertension and left ventricular hypertrophy by activating the renin-angiotensin-aldosterone pathway. It results in a rise in the hormone parathyroid, which raises insulin resistance and is linked to diabetes, hypertension, inflammation, and an increased risk of cardiovascular disease [27].

CONCLUSION

The study concluded that after 6 months of course of administration with vitamin D supplementing with n-3 fatty acids in the mentioned dosage among initially healthy adults resulted in a slight but statistically insignificant decrease in a composite endpoint of major CVD events but a statistically significant reduction was found in cardiovascular mortality and ischemic stroke as compared to healthy controls. The study further decreases in other coronary outcomes, but no decrease in stroke, cancer mortality and coronary heart disease were found statistically. A putative cardioprotective effect for n-3 fatty acids in a typical-risk scenario is supported by the decrease in total MI, particularly in African Americans and those with limited dietary fish intake or cardiovascular risk factors. In initially healthy people, daily high-dose vitamin D supplementation did not lower the incidence of major CVD events or secondary CVD endpoints, but it did provide a promising signal for lowering cancer mortality. Updated meta-analyses of these therapies have been influenced by VITAL and other recent trials, and they suggest that the benefit-risk pattern may differ by subgroup. Which individuals are most likely to see a net benefit from these supplements needs more investigation.

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