The role of omega-3 fatty acid supplementation on glycemic control and lipid profiles in reproductive-aged women with pre-diabetes.

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Research Article

Keywords: omega-3 fatty acid, glycemic control, lipid profile, reproductive-aged women, pre-diabetes

Posted Date: December 18th, 2024

DOI: https://doi.org/10.21203/rs.3.rs-5381717/v1

Additional Declarations: No competing interests reported.

Abstract

Background: Prediabetes is a precursor to type 2 diabetes and healthy interventions results in delay or postponing. To evaluate the benefits of omega-3 fatty acid supplements in reducing glycemic and lipid profiles in reproductive-aged women with Prediabetes.

Material and Methods- This is a Randomized placebo Controlled Trial conducted on 90 patients at a tertiary Hospital and Research Centre, in India. After randomization one group (n=45) received placebo and the other received (n=45) Omega3 fatty acid supplement (1000mg) twice daily. Blood samples were collected from all participants in the morning after 12 h of fasting for lipid profile. The insulin resistance was determined using the homeostatic model assessment of insulin resistance (HOMA-IR) index, and the beta-cell function using the HOMA-B index.

Results- After a follow-up perid of three months subsequent to the drug intervention, the average FBS showed a significant reduction to 99.5 ± 8.6 ($p < 0.0001$) in post group. Conversely, there was no notable alteration observed in the average PPBS, HbA1c, and fasting insulin levels, the mean HDL, LDL, VLDL, between the Pre and post groups. The average HOMA-IR and average TGL were decreased in the Post group ($p < 0.0001$).

Conclusion- In the present study omega 3 fatty acid supplementations improved fasting blood sugar, triglycerides and HOMA-IR in reproductive-aged women with pre-diabetes. Considering the impact of Prediabetes in reproductive health and its outcome, omega-3 supplementation, therefore, can be recommended as a therapeutic option for glycemic control in these individuals.

Summary

In conclusion, this study adds to the growing body of evidence that supports the potential benefits of supplementing with omega-3 fatty acids in individuals with a diagnosis of type 2 diabetes mellitus (T2DM). Although there was minimal impact observed on body mass index (BMI) and waist circumference (WC), our findings are consistent with existing literature that highlights positive effects on various metabolic parameters. The study underscores the potential of omega-3 supplementation in improving glycemic control, as indicated by differences in fasting and postprandial blood glucose levels. Furthermore, the observed changes in triglyceride levels, without any negative effects on cholesterol profiles, further emphasize the favorable role of omega-3 supplements. These results, in line with previous research, provide support for further investigation into the use of omega-3 supplementation as an adjunctive therapy for the management of T2DM.

1. Introduction

Pre-diabetes is an intermediary state situated between the regular levels of glucose in the bloodstream and the onset of type 2 diabetes.[1] It is worth noting that individuals with pre-diabetes are susceptible to the development of diabetes in long term. It has been observed that annually approximately 5 to 10

percent of prediabetes population transition to type 2 diabetes occurs.[2] Studies have shown that in 2015, around 318 million individuals globally were affected by pre-diabetes; projections indicate that this number will increase to 471 million by the year 2035. [3] The prevalence of nephropathy, retinopathy, and macrovascular complications has been demonstrated in individuals with pre-diabetes.[4] Studies on reproductive health of women indicate that is negatively impacted by insulin resistance, leading to alterations in menstrual patterns, decreased fertility, sexual dysfunction, urinary and vaginal infections, urine incontinence, and depression. Furthermore, the risk of breast and ovarian cancer is heightened due to increased insulin resistance. Additionally, this particular population is at risk of developing gestational diabetes during pregnancy. [4–5]

There has been evidence underlying that the consumption of fish and shellfish in the Finnish population has the potential to significantly reduce the prevalence of T2DM. This positive effect is linked to the presence of omega three fatty acids, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in fish, which are homologous polyunsaturated fatty acids (PUFAs). However, recent studies have presented conflicting views on the benefits of omega-3 supplementation in individuals with diabetes, leading to a possible underestimation of its potential value in preventing type 2 diabetes. [6–7]

These contradictory findings emphasize the need for further investigation into the impact of omega-3 supplementation on glucose regulation. The variations in results may be attributed to differences in research methodologies, such as trial design, duration, the ethnic background of participants, and the dosage administered. Therefore, it is challenging to draw definitive conclusions regarding the advantages of omega-3 supplementation in diabetes patients, highlighting the importance of a comprehensive meta-analysis as a valuable reference for healthcare professionals.[8–9]

The initial systematic investigation, which was published in 2000, discovered that omega-3 exhibited no detrimental impact on the glycemic management of individuals with diabetes. [10] Later a comprehensive review, where they determined that omega-3 supplementation leads to a reduction in plasma triglyceride (TG) levels, but does not exhibit any statistical significance in relation to insulin or glucose.[11] These previous systematic studies provided inconclusive evidence regarding dietary recommendations for patients with diabetes. As a result, we conducted a thorough randomized clinical trial (RCT) at a tertiary hospital in India to investigate the advantageous effects of omega-3 fatty acids in women of reproductive age who have Prediabetes.

2. Material and methods

2.1.Study design

A Randomized Placebo Control Trial was conducted for Prediabetic women aged 18-45 at the SRM Medical College Hospital and Research Centre for three months during January 2021 to June 2022. 90 study samples were assigned to two groups after receiving the written consent from the patients. The

ethical committee of SRM Medical College Hospital and Research Centre approved the study (Ethical Clearance No: 2386/IEC/2021).

The inclusion criteria were 1) Females of reproductive aged 18-45 years with Prediabetic HbA1c within the range of 5.7-6.4. 2) Fasting Blood Sugar between 100-125 mg/dL or Post-Prandial between 140-199 mg/dL 3) Willingness to participate in the study and using omega 3 fatty acid supplements. The exclusion criteria were 1) Diabetes type 1 or 2 and underlying diseases 2) Using oral hypoglycemic agents or lipid-lowering agents 3) Having used omega-3 supplements over the last six months 4) Acute Critical Illness 5) Coronary Artery disease (CAD) 6) Chronic Kidney disease CKD stage ≥ III 7) Pregnancy or breastfeeding 8)Non-willingness to the medication administration protocols.

Initial sampling involved all female reproductive age patients referred for diabetes screening (120 patients). Based on the inclusion and exclusion criteria 90 patients were screened and randomised into two groups. The group I Healthy individuals with pre-diabetes (N=45) with no documented diseases received 1000mg omega-3 fatty acid supplementation -360 mg eicosapentaenoic acid (EPA) and 240 mg docosahexaenoic acid (DHA) twice daily for three months and the group II Healthy individuals with pre-diabetes (N=45) with no documented disease received 1000mg of Placebo (Capsugel (Lonza), with inert ingredients like cellulose and glycerin.) twice daily for three months. The supplements and placebo were of similar colour, shape and size and identified with letters A and B and intervention group was blinded to the participants, study invstigators and statistician.

2.2 Anthropometric Indices like Height, Weight, and Waist Circumference were collected and Body mass index (BMI) was calculated in all patients (BMI = weight [kg]/height [m2])

2.3 Laboratory measurements: Fasting blood samples were collected from all participants after 12 h of fasting. Routine tests including Fasting Blood Sugar (FBS), Postprandial Blood Sugar (PPBS), HbA1c, Fasting Lipid Profile- Total Cholesterol, HDL, LDL, VLDL, Triglycerides, Serum Creatinine and eGFR were measured. Fasting blood insulin (FBI) was measured. The insulin resistance was determined using the HOMA-IR index, and the beta-cell function using the HOMA-B index as follows:

HOMA−IR=[FBI(μU/mL) ×FBS (mg/mL)]/405

HOMA−B=[(FBI(μU/mL) ×360)/ (FBS (mg/mL) −63)] %.

2.4. Statistical analysis of the study:

Mean (Standard Deviation) and Number (Percentage) were used to describe the distributions of the Continuous and Categorical variables, respectively. In addition, one-way analysis of variance (ANOVA) and the Chi-square test (Chi-square) were used to compare continuous and categorical variables across groups at baseline. Data was analyzed using SPSS-24 software version 20.0. Test results were deemed to be significant at 95% confidence intervals with P ≤.05. The intent-to-treat analysis was used for all analyses.

3. Results

Of the total of 90 patients, 45 participants were assigned to receive omega 3 supplements while the remaining 45 were given a placebo (Fig. 1). These study subjects were then monitored for a duration of 3 months. Prior to the intervention, the average age, height, weight, BMI, and waist circumference did not exhibit any statistically significant differences between the group receiving the drug and the group receiving the placebo (Table 1). No side effects were reported by the subjects following consumption of the supplements and placebo.

Table 1
Demographics, anthropometric indices and lipid profile of the study groups before (Pre group) and after (Post group) Intervention

Group		Drug	Placebo	Pvalue
Age	Pre group	35.29 ± 6.65	33.12 ± 8.18	0.14
Height (cm)	Pre group	161.31 ± 5.16	159.9 ± 5.91	0.2
Weight (kg)	Pre group	66.08 ± 8.6	65.02 ± 9.41	0.551
	Postgroup	65.93 ± 8.42	66.1 ± 8.89	0.929
	P value	0.581	0.422	
BMI	Pre group	25.25 ± 3.72	25.58 ± 3.99	0.984
	Postgroup	25.3 ± 3.73	25.72 ± 3.94	0.612
	P value	0.365	0.002	
Waist Circumference (cm)	Pre group	84.5 ± 14.63	83.04 ± 8.35	0.424
	Postgroup	84.07 ± 14.64	82.67 ± 8.14	0.579
	P value	< 0.0001	< 0.0001	
Total Cholesterol	Pre group	231.76 ± 55.98	237 ± 41.24	0.656
	Postgroup	228.18 ± 57.26	234.93 ± 41.28	0.523
	P value	< 0.001	< 0.001	
HDL	Pre group	36.73 ± 6.95	35.76 ± 6.44	0.371
	Postgroup	36.33 ± 7.26	35.84 ± 6.54	0.738
	P value	0.267	0.813	
LDL	Pre group	97.96 ± 38.78	91.07 ± 26	0.369
	Postgroup	97.98 ± 38.08	91.09 ± 25.06	0.314
	P value	0.936	0.983	
TGL	Pre group	206.47 ± 55.33	207.27 ± 27.22	0.761
	Postgroup	177.56 ± 34.58	199.4 ± 28.31	< 0.001
	P value	< 0.0001	< 0.001	
VLDL	Pre group	17.69 ± 5.81	18.53 ± 6.99	0.594
	Postgroup	17.78 ± 6.25	18.87 ± 7.73	0.464
		0.528	0.041	

3.1. Effects on Anthropometric indices

The effects of supplements and placebo groups before and after intervention is given in Table 1. Following the 3-month follow-up period, the data indicated that there were no alterations in the mean BMI or waist circumference within the groups before and after the administration of the drugs. The mean BMI in the drug intervention pre group was 25.25 ± 3.72, and in the post group was 25.30 ± 3.73, which is not statistically significant. The mean BMI in the Placebo pre group was 25.58 ± 3.99, and in the post group was 25.72 ± 3.94, which is statistically significant, with a p-value of 0.002. The mean waist circumference in the group 1 drug intervention of pre group was 84.50 ± 14.63, and in the post group was 84.07 ± 14.64, that is statistically significant with a p-value of < 0.0001.

3.2. Effects on Lipid profile

Additionally, the mean values of Total Cholesterol, HDL, LDL, and VLDL did not show any notable variations between the drug group and the placebo group prior to the intervention (Table 1). The mean values of HDL, LDL, and VLDL did not exhibit any statistically significant differences between the Pre group and the Post group. However, the mean TGL in the Pre group was measured as 199.4 ± 28.3, while in the Post group it showed a decrease to 177.56 ± 34.6 ($p < 0.0001$) (Table 1). The various variables associated with lipid profile, such as total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TGL), and very low-density lipoprotein (VLDL), remained largely consistent from the baseline to the follow-up period, except for TGL. At baseline, the TGL values were 177.56 and 199.4 for the drug and placebo groups respectively, whereas after the follow-up period, the values were 208.37 and 205.71 for the drug and placebo groups respectively. The pre and post-data of the placebo group patients exhibited a significant ($p < 0.0001$) change in the TC and TGL variables. On the other hand, the drug group experienced a significant change ($p < 0.0001$) only in the TGL parameter.

3.3. Effects on Placebo group

Likewise, the glycemic parameters including mean FBS, PPBS, Fasting Insulin, HOMA-IR, and HOMA B did not undergo any significant changes between the drug group and the placebo group (Table 2). Interestingly, the mean FBS in the Pre group was recorded as 125.5 ± 10.5, and it demonstrated a significant reduction in the Post group with a mean of 99.5 ± 8.6 ($p < 0.0001$) whereas the placebo group showed a significant increase in Placebo group post intervention. Conversely, there were no changes observed in the mean values of PPBS, HbA1c, and fasting insulin between the Pre group and the post-treatment group. Furthermore, the mean HOMA-IR in the Pre group was 4.22 ± 1.6, which decreased to 3.06 ± 1.45 in the Post group ($p < 0.001$) (Table 2).

Table 2
Clinical Characteristics of the Study Groups after the intervention

Group		Mean	Std. Deviation	P value
Weight (kg)	Drug	65.93	8.42	0.929
	Placebo	66.10	8.89	
BMI	Drug	25.30	3.73	0.612
	Placebo	25.72	3.94	
Waist Circumference (cm)	Drug	84.07	14.64	0.579
	Placebo	82.67	8.35	
FBS	Drug	99.56	8.59	0.000
	Placebo	125.51	10.54	
PPBS	Drug	154.13	19.93	0.236
	Placebo	158.71	16.26	
Hba1C	Drug	6.24	0.35	0.899
	Placebo	6.25	0.32	
Total Cholesterol	Drug	228.18	57.26	0.523
	Placebo	234.93	41.28	
HDL	Drug	36.33	7.26	0.738
	Placebo	35.84	6.54	
LDL	Drug	97.98	38.08	0.314
	Placebo	91.09	25.06	
TGL	Drug	177.56	34.58	0.001
	Placebo	199.40	28.31	
VLDL	Drug	17.78	6.25	0.464
	Placebo	18.87	7.73	
Fasting Insulin	Drug	12.27	5.12	0.203
	Placebo	13.69	5.34	
HOMA-IR	Drug	3.06	1.45	< 0.0001
	Placebo	4.22	1.60	
HOMA-B	Drug	22.55	11.42	0.264

Group		Mean	Std. Deviation	P value
	Placebo	25.46	13.27	

4. Discussion

T2DM is a metabolic disorder characterized by elevated blood glucose levels, insulin resistance, and dysfunction of β-cells. The global incidence of this condition is increasing at an alarming rate .[2]. Epidemiological and clinical investigations have suggested that lifestyle factors, particularly daily dietary choices, play a significant role in the development and management of T2DM. Healthcare professionals and nutrition experts are increasingly recognizing the potential of a balanced diet to improve glycemic control. Research indicates that incorporating fish and shellfish into the diet may have a profound impact on reducing the prevalence of T2DM in the general population.[10–11]

The patient demographics utilized in the present study were comparable to those reported in previous studies. [12–14] Omega-3 fatty acid supplementation did not lead to a decrease in body mass index (BMI) in either group of patients. However, there are contradictory studies were, a reduction in BMI was observed following omega-3 fatty acid supplementation.[15]. The current investigation found minimal influence of omega-3 fatty acid supplementation on waist circumference (WC). In contrast, a significant decrease in WC after omega-3 fatty acid supplementation was observed. Multiple studies have also documented the beneficial effects of omega-3 fatty acids on fasting glucose levels, triglyceride levels, insulin resistance, and waist circumference. [14]

While the baseline values of fasting blood sugar (FBS) remained unaffected, a notable disparity was observed in FBS following the administration of omega-3 fatty acid supplementation. A similar observation was also documented for postprandial blood sugar (PPBS). A study showed the effects of administering pregnant women with 50,000 IU of vitamin D every two weeks and 1000 mg of omega-3 twice daily for a period of six weeks. The co-supplementation was found to have positive effects on glycemic control, triglyceride levels, and very low-density lipoprotein (VLDL-c) levels. These findings align with the effects observed in omega-3 co-supplementation with regards to fasting insulin and glucose levels.[16–17]

Studies have streesed that diabetic patients should consider taking omega-3 supplements due to their ability to lower triglyceride levels without negatively impacting glycemic control and oxidative stress. [18]. Our study yielded similar results, as TGL levels decreased while total cholesterol, LDL, and HDL levels remained unchanged.

The patients in the drug group exhibited a noteworthy alteration in the HOMA-IR and HOMA-B parameters, as indicated by the pre and post-data. A similar significant change in the HOMA-IR parameter in their study, aligning with our findings. [19] On the other hand, a study showed that the supplementation of omega-3 fatty acids in women of reproductive age led to improvements in fasting

glucose, insulin, HDL-C, and HOMA-B values.[12] Several studies also reported a beneficial effect of omega-3 fatty acids in improving fasting glucose, triglyceride levels, insulin resistance, and waist circumference.[14]

Our study is not without limitations. They include a small sample size and the absence of Continuous Glucose Monitoring (CGM), which resulted in the unavailability of pre and post-meal data. These limitations might explain the slight increase in HbA1c observed in the drug group.

Conclusion

This study has provided insight into the advantageous impacts of omega-3 fatty acid supplementation on enhancing the levels of fasting and post-prandial blood glucose, triglycerides, HOMA-B, and HOMA-B in women of reproductive age who have pre-diabetes. Given that omega-3 fatty acids have the potential to enhance glycemic control, lipid metabolism, and oxidative stress in women with gestational diabetes or pre-diabetes, we propose omega-3 as a viable treatment option for pre-diabetes instead of traditional oral hypoglycemic agents, which may have adverse effects on pregnant women.

Declarations

Author Contribution

ASY - Conceptualization; Data curation; Formal analysis, Writing - original draftNDC - Investigation; MethodologyGS - Writing - review & editingRRL - Writing - review & editingMP - Supervision; Validation; VisualizationJS K - Supervision; Validation

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Figures

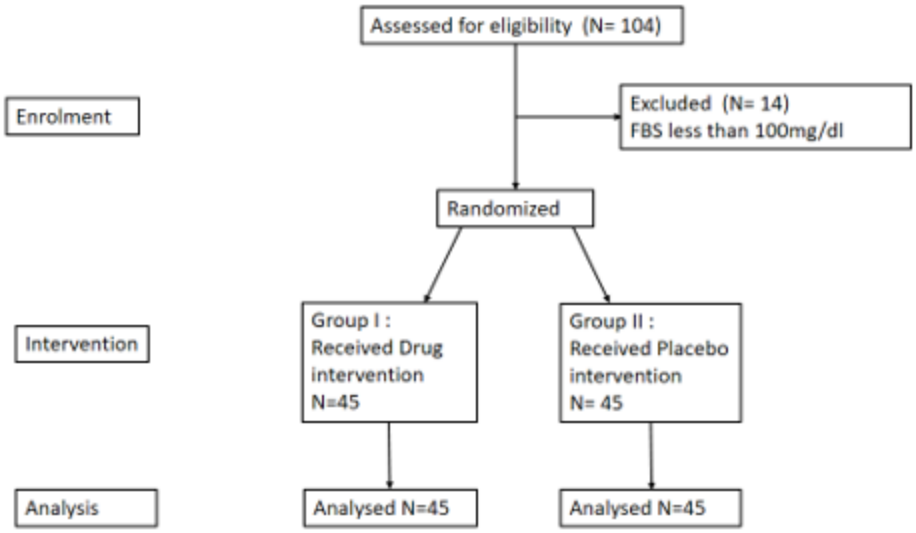

Figure 1

Flow chart of the experiment