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THE EFFECT OF OMEGA 3 POLYUNSATURATED FATTY ACID ORAL SUPPLEMENT ON PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE IN NAJAF CITY

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ABSTRACT

Background: Nonalcoholic fatty liver disease (NAFLD) has emerged as one of the most prevalent chronic liver disorders worldwide, affecting approximately 25% of the global population. It encompasses a range of liver conditions, from simple steatosis, characterized by the accumulation of fat in the liver without significant inflammation, to nonalcoholic steatohepatitis (NASH). **Aims of the study**: To evaluate the efficacy of Omega 3 PUFA supplementation of daily 1 gram for 3 months in patients with non-alcoholic fatty liver disease. **Method:** A single-blind, randomized trial in Najaf, Iraq (March–Sept 2024) assessed Omega-3 PUFA (1g daily) versus placebo in 118 NAFLD patients over 12 weeks. Outcomes included liver function (ALT, AST, TG, FBS, cholesterol) and steatosis grading via ultrasound. Omega-3 supplementation showed potential benefits in improving biochemical and structural liver health. **Results:** The study found significant improvements in the Om3TP group after Omega-3 supplementation. BMI, waist circumference, triglycerides, ALT, AST, and ultrasound measurements significantly decreased ($p<0.05$), while HDL increased and fasting blood sugar reduced. No significant changes were observed in total cholesterol or LDL levels. The intervention effectively improved key health markers in NAFLD patients. **Conclusion:** The study found that omega-3 PUFA supplementation reduces triglycerides, liver enzymes (ALT and AST), and hepatic fat buildup in MASLD patients. It also lowers fasting blood sugar and raises BMI and HDL cholesterol. Total cholesterol, LDL, and waist circumference did not improve.

KEYWORDS: Omega 3, Polyunsaturated, Fatty Acid, Oral Supplement, Non-Alcoholic Fatty Liver Disease.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has materialized as one of the commonest chronic liver disorders globally, unfavorably impacting about 25% of the population. It ranges from simple steatosis-single liver fat infiltration without significant inflammation-to nonalcoholic steatohepatitis (NASH).[1] Relatively related is the metabolic syndrome: obesity, insulin resistance, diabetes mellitus type 2, dyslipidemia, and hypertension together to form quite a worrisome conglomerate for public health.[2] Based on this association between metabolic dysfunction and hepatic steatosis, in 2023, the term MASLD or metabolic dysfunction-associated steatotic liver disease replaced 'nonalcoholic fatty liver diseases' (NAFLD) and NASH with metabolic dysfunction-associated steatohepatitis (MASH) to better describe this entity.[3,4] The disease ranges from the presence of hepatic steatosis to various other severities like steatohepatitis, fibrosis up to cirrhosis.[5] Mafia is a disease entity characterized by liver fat accumulation related to metabolic dysfunctions like obesity, type 2 diabetes, and/or the metabolic syndrome. The substitution of the previously used nomenclature "nonalcoholic fatty liver disease" (NAFLD) makes it a metabolic-rooted entity. Its features include hepatic steatosis and a metabolic risk factor as a minimum criterion for diagnosis. It has practically become the world's top most cause of chronic liver diseases and has enormous implications in terms of liver-related as well as cardiovascular morbidity and mortality.[6] All this time omega-PUFAs albeit vitamin E, which functions in lipid metabolism and metabolism-related oxidative stress regulators, are crucial players in liver health management as a whole.[7] The deficiency or

imbalance of it may accelerate the development of fatty liver diseases such as steatosis and inflammation.[8] Resmetirom, also referred to as Rezdiffra, is a novel drug for MASLD that selectively agonists thyroid hormone receptor-beta (THR-β). Resmetirom FDA was very recently approved in 2024 for noncirrhotic NASH with F2-F3 fibrosis; it reduces liver fat, fibrosis as well as inflammation. GI issues and changes in liver enzymes may occur due to resmetirom; therefore, its usage needs to be monitored.[9] Most omega-3 PUFAs originate from marine sources, including EPA and DHA. These acids decrease triglycerides, improve insulin, and reduce inflammation. These fatty acids improve hepatic fat metabolism, decrease inflammation, and improve liver enzyme profiles, making them a viable NAFLD (MASLD) treatment.[10] Omega-3 PUFAs impact peroxisome proliferatore-activated receptors (PPARs) and sterol regulatory element-binding proteins (SREBPs) to alter lipid metabolism. This alteration shifts hepatic lipid metabolism from lipogenesis to improved fatty acid oxidation, preventing fat storage.[11] Omega-3 PUFAs also reduce pro-inflammatory cytokines and oxidative stress, which are linked to MASLD, particularly MASH.[12] People with MASLD who took omega-3 PUFA supplements had significant decreases in liver fat, blood lipids, and liver damage markers such serum aminotransferases.[13] The insulin sensitivity which is a crucial phenomenon in the pathogenesis of MASLD has been improved. Recommended dose and duration of omega-3 PUFA supplementation as investigated in different trials are varied. While some trials have demonstrated significant therapeutic benefits, others have shown a minimal or no effect, indicating the need for further research to develop and implement protocols.[14] The aim of study is to assess the effect of Omega 3 PUFA supplementation at a dose of 1gm per day for 3 months on patients with non-alcoholic fatty liver disease.

PATIENT AND METHOD

One hundred eighteen patients diagnosed with MASLD were included in the study. They were randomly allocated to an omeg3 treated patient (Om3TP) (65 patients) and a placebo treated patient (PTP) (53 patients), from Gastroenterology and Hepatology Hospital in Najaf city. Omega-3 PUFA supplementation was given to Om3TP, at a dosage of 1 g per day for 12 weeks, because the therapeutic efficacy of Omega-3 PUFAs in liver diseases has been documented in the literature. The PTP was given a placebo that retained the same appearance and method of administration as that of the Omega-3 PUFA group. Eligible participants underwent baseline assessments, including anthropometric measures, fasting blood sugar, liver enzyme tests and ultrasound imaging, to establish initial liver fat content and liver function markers. US was done by single radiologist follow the criteria of fatty liver diagnosed by US which include the following.

Grade 0: steatosis absent.

Grade 1: mild steatosis (lightly and homogen-eously increased liver echotexture, with patent intra-hepatic vascular pattern; posterior attenuation absent).

Grade 2: moderate steatosis (moderate increase of liver echotexture; partial dimming of the vessels; early posterior attenuation).

Grade 3: severe steatosis (diffuse increase of liver echogenicity, with no longer visible intra-hepatic ves-sels; heavy posterior attenuation).

Improvement was assessed according to these criteria. Any decreasing in grading considered improvement.

These two groups selected according to the following inclusion criteria, which are.

1. Age 18 – 65 years
2. Clinical diagnosis based on ultrasound US and lab tests
3. Willingness to participate

The exclusion criteria

1. A history of alcohol intake exceeding 30 g per day in male while in female 20 g
2. The use of drugs that are known to be associated with liver steatosis,
3. Undernutrition,
4. Chronic viral hepatitis, B and C
5. Chronic liver disease of other etiologies (autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, hereditary haemochromocytosis, Wilson's disease, alpha 1 antitrypsin deficiency, and coeliac disease).
6. Pregnant and lactating women.

The study was designed to ensure participants remained unaware of their group assignment, employing a single-blind approach. Both groups were provided with similar dietary and lifestyle recommendations to minimize external influences on liver function and lipid profiles. Compliance with supplementation was monitored through biweekly follow-up calls and tablet counts conducted at each clinical visit.

The primary outcomes were measured through changes in liver function and structure, as assessed by biochemical tests and ultrasound imaging. Blood tests measured liver enzymes (alanine transaminase [ALT] and aspartate transaminase [AST]), triglycerides (TG), fasting blood sugar (FBS), and cholesterol levels both before and after the intervention. Ultrasound imaging was used to assess hepatic steatosis and fat accumulation in the liver at baseline and after the intervention. These assessments were selected to monitor both biochemical and structural changes in liver health and evaluate the effectiveness of Omega-3 PUFA supplementation in MASLD management. Fibro scan was not used as a tool for dx and follow up in this study as it is not easy accessible for all patient for its low availability and high cost. The collected data underwent statistical analysis using SPSS software. Differences in liver enzyme levels,

lipid profiles, and ultrasound measures between the two groups were analyzed using t-tests and Mann-Whitney U tests for continuous data. Statistical significance was set at $p < 0.05$. Data were presented as mean values with standard deviations for continuous variables and percentages for categorical variables. Informed consent was obtained from all participants, who were informed about the study's purpose, duration, procedures, and potential risks. Ethical approval was secured from the institutional ethics committee before initiating the trial. Participants were assured of confidentiality and informed of their right to withdraw from the study at any time without any effect on their medical care.

RESULTS

Age Distribution

The mean age of the participants ranging from 25 years with oldest 65 years' old

- **The patient's age between 20-29 years** is 9.2% of the Om3TP group falls, while 15.1% of the **PTP** group belongs to this age group
- **The patient's age between 30-39 years**: The Om3TP group has 26.2% of patients, compared to 20.8% in the **PTP** group.
- **The patient's age between 40-49 years**: This age group has the highest representation, with 33.8% in the Om3TP group and 30.2% in the **PTP** group.
- **The patient's age between 50-59 years**: 18.5% of the Om3TP group and 20.8% of the **PTP** group are in this age range.
- **≥60 years**: 12.3% of the Om3TP group and 13.2% of the **PTP** group fall in this category.
- The most common age group is between 40-49 is in both groups.

Gender Distribution

- **The Females in the study:** 58.5% in the Om3TP group and 56.6% in the **PTP** group.
- **The Males in the study**: 41.5% in the Om3TP group and 43.4% in the **PTP** group.
- There is a balanced distribution in gender, with a slightly higher percentage of females in both groups.

Table 1: shows a comparison of patients' distribution among the two groups (Om3TP vs PTP) which are statically matched based on their age groups and gender.

Variables		Groups	
		Om3TP	PTP
Age groups	***20-29***	6 (9.2%)	8 (15.1%)
	30-39	17 (26.2%)	11 (20.8%)
	40-49	22 (33.8%)	16 (30.2%)
	50-59	12 (18.5%)	11 (20.8%)
	≥60	8 (12.3%)	7 (13.2%)
Gender	***Females***	38 (58.5%)	30 (56.6%)
	Males	27 (41.5%)	23 (43.4%)
	Total	65 (100.0%)	53 (100.0%)

BMI (Body Mass Index) after Intervention

- **PTP Group**: Mean = 35.93, SD = 5.13
- **Om3TP Group**: Mean = 33.90, SD = 5.59
- **P-value** = 0.04, indicating a statistically significant reduction in BMI in patient treated by omega 3 vs the PTP group after the intervention.

WC (Waist Circumference) After Intervention

- **PTP Group**: Mean = 101.60, SD = 9.56
- **Om3TP Group**: Mean = 100.40, SD = 10.90
- **P-value** = 0.5, suggesting no significant reduction in waist circumference between the two groups.

TC (Total Cholesterol) After Intervention

- **PTP Group**: Mean = 193.35, SD = 28.07
- **Case Group**: Mean = 186.98, SD = 20.10
- **P-value** = 0.2, indicating no statistically significant reduction in total cholesterol levels between the two groups.

LDL (Low-Density Lipoprotein) after Intervention

- **PTP Group**: Mean = 118.01, SD = 21.79
- **Om3TP Group**: Mean = 133.30, SD = 150.61
- **P-value** = 0.4, suggesting no significant reduction in LDL levels between the two groups.

HDL (High-Density Lipoprotein) After Intervention

- **PTP Group**: Mean = 47.52, SD = 4.63
- **Om3TP Group**: Mean = 47.80, SD = 6.27
- **P-value** = 0.7, indicating no significant reduction in HDL levels between the two groups.

TG (Triglycerides) After Intervention

- **PTP Group**: Mean = 147.88, SD = 35.44
- **Om3TP Group**: Mean = 123.78, SD = 34.37
- **P-value** = 0.0001, showing a highly significant reduction in triglyceride levels, in patient treated by omega 3 vs the PTP group after the intervention.

ALT (Alanine Aminotransferase) After Intervention

- **PTP Group**: Mean = 47.50, SD = 19.00
- **Case Group**: Mean = 28.81, SD = 9.26
- **P-value** = 0.0001, indicating a highly significant reduction in ALT levels in patient treated by omega 3 vs the PTP group after the intervention.

AST (Aspartate Aminotransferase) After Intervention

- **PTP Group**: Mean = 33.69, SD = 13.22
- **Case Group**: Mean = 18.93, SD = 5.88
- **P-value** = 0.0001, showing a highly significant reduction in AST levels in patient treated by omega 3 vs the PTP group after the intervention.

FBS (Fasting Blood Sugar) After Intervention

- **PTP Group**: Mean = 87.60, SD = 15.37
- **Om3TP Group**: Mean = 90.20, SD = 12.28
- **P-value** = 0.05, indicating significant reduction in fasting blood sugar levels.

US (Ultrasound Measurement) After Intervention

- **PTP Group**: Mean = 0.94, SD = 0.1
- **Om3TP Group**: Mean = 0.44, SD = 0.08
- **P-value** = 0.001, indicating a highly significant reduction in ultrasound measurements between the two groups.

Therefor Table 2 reveals significant differences between the Om3TP and **PTP** groups in several clinical parameters after the intervention. Specifically, the Om3TP group has significantly lower triglycerides (TG), liver enzymes (ALT, AST), and ultrasound measurements (US) compared to the **PTP** group. BMI and fasting blood sugar (FBS) also show significant or significant differences, while other parameters like waist circumference (WC), total cholesterol (TC), LDL, and HDL did not differ significantly between the groups.

Table 2: Shows The Differences In The Mean Values Of Various Clinical Parameters Between The Om3TP And PTP Groups After The Intervention, Using Mean Values, Standard Deviations, And P-Values To Determine Statistical Significance.

	Group	N	Mean GH	Std. Deviation	P-value
BMI after	**PTP**	53	35.93	5.13	**0.04**
	Om3TP	65	33.90	5.59	
WC after	**PTP**	53	101.60	9.56	0.5
	Om3TP	65	100.40	10.90	
TC after	**PTP**	53	193.35	28.07	0.2
	Case	65	186.98	20.10	
LDL after	**PTP**	53	118.01	21.79	0.4
	Case	65	133.30	150.61	
HDL after	**PTP**	53	47.52	4.63	0.7
	Om3TP	65	47.80	6.27	
TG after	**PTP**	53	147.88	35.44	**0.0001**
	Om3TP	65	123.78	34.37	
ALT after	**PTP**	53	47.50	19.00	**0.0001**
	Om3TP	65	28.81	9.26	
AST after	**PTP**	53	33.69	13.22	**0.0001**
	Om3TP	65	18.93	5.88	
FBS after	**PTP**	53	87.60	15.37	**0.05**
	Om3TP	65	90.20	12.28	
US after	**PTP**	53	0.94	0.1	**0.001**
	Om3TP	65	0.44	0.08	

BMI (Body Mass Index) Before and After Intervention

- **Before**: Mean = 35.83, SD = 5.49
- **After**: Mean = 33.90, SD = 5.59
- **P-value** = 0.0001, indicating a highly significant reduction in BMI after the intervention.

WBC (Waist Circumference) Before and After Intervention

- **Before**: Mean = 103.66, SD = 11.44
- **After**: Mean = 100.40, SD = 10.90
- **P-value** = 0.0001, showing a significant reduction in waist circumference after the intervention.

TC (Total Cholesterol) Before and After Intervention

- **Before**: Mean = 190.58, SD = 30.94
- **After**: Mean = 186.98, SD = 20.10
- **P-value** = 0.2, indicating no significant change in total cholesterol levels.

LDL (Low-Density Lipoprotein) Before and After Intervention

- **Before**: Mean = 115.56, SD = 23.80
- **After**: Mean = 133.30, SD = 18.68
- **P-value** = 0.3, suggesting no significant change in LDL levels.

HDL (High-Density Lipoprotein) Before and After Intervention

- **Before**: Mean = 45.86, SD = 10.99
- **After**: Mean = 47.80, SD = 6.27

- **P-value** = 0.04, showing a significant increase in HDL levels after the intervention.

TG (Triglycerides) Before and After Intervention
- **Before**: Mean = 150.80, SD = 46.62
- **After**: Mean = 123.78, SD = 34.37
- **P-value** = 0.0001, indicating a highly significant reduction in triglyceride levels after the intervention.

ALT (Alanine Aminotransferase) Before and After Intervention
- **Before**: Mean = 54.16, SD = 20.80
- **After**: Mean = 28.81, SD = 9.26
- **P-value** = 0.0001, showing a highly significant reduction in ALT levels.

AST (Aspartate Aminotransferase) Before and After Intervention
- **Before**: Mean = 37.75, SD = 13.74
- **After**: Mean = 18.93, SD = 5.88
- **P-value** = 0.0001, indicating a highly significant reduction in AST levels after the intervention.

FBS (Fasting Blood Sugar) Before and After Intervention
- **Before**: Mean = 92.84, SD = 17.47
- **After**: Mean = 90.20, SD = 12.28
- **P-value** = 0.04, indicating a significant reduction in fasting blood sugar after the intervention.

US (Ultrasound Measurement) Before and After Intervention
- **Before**: Mean = 1.18, SD = 0.10
- **After**: Mean = 0.44, SD = 0.08
- **P-value** = 0.0001, indicating a highly significant reduction in ultrasound measurements after the intervention.

Therefore, Table 3 demonstrates statistically significant improvements in several key health indicators in the Om3TP group following the intervention. BMI, waist circumference (WC), triglycerides (TG), ALT, AST, and ultrasound measurements (US) all showed significant reductions. HDL increased significantly, which is a positive outcome, while fasting blood sugar (FBS) also showed a significant reduction. There were no significant changes in total cholesterol (TC) or LDL levels. Overall, the intervention appears to have had a positive impact on the health markers of the Om3TP group.

Table 3: provides the comparison of mean values for several health indicators before and after the intervention for the Om3TP group only.

	Group	N	Mean GH	Std. Deviation	P-value
BMI	before	65	35.83	5.49	**0.0001**
	after	65	33.90	5.59	
WC	before	65	103.66	11.44	**0.0001**
	after	65	100.40	10.90	
TC	before	65	190.58	30.94	0.2
	after	65	186.98	20.10	
LDL	before	65	115.56	23.80	0.3
	after	65	133.30	18.68	
HDL	before	65	45.86	10.99	**0.04**
	after	65	47.80	6.27	
TG	before	65	150.80	46.62	**0.0001**
	after	65	123.78	34.37	
ALT	before	65	54.16	20.80	**0.0001**
	after	65	28.81	9.26	
AST	before	65	37.75	13.74	**0.0001**
	after	65	18.93	5.88	
FBS	before	65	92.84	17.47	**0.04**
	after	65	90.20	12.28	
US	before	65	1.18	0.10	**0.0001**
	after	65	0.44	0.08	

DISCUSSION

The study under discussion evaluates the impact of omega-3 polyunsaturated fatty acid (PUFA) supplementation on patients with Metabolic Associated Fatty Liver Disease (MAFLD), focusing on various clinical parameters. The findings indicate significant improvements in several health markers, aligning with existing works on the benefits of omega-3 PUFAs in liver health.

Lipid profile: As the study reports a significant decrease in triglyceride (TG) levels among patients receiving omega-3 PUFA supplementation. This outcome is consistent with a meta-analysis of randomized controlled trials, which concluded that omega-3 PUFAs effectively

reduce TG levels in individuals with non-alcoholic fatty liver disease (NAFLD).[15] The hypolipidemic effect of omega-3 PUFAs is attributed to their ability to inhibit hepatic lipogenesis and enhance fatty acid oxidation, leading to lower plasma TG concentrations.[15] The observed increase in HDL levels post-supplementation is noteworthy, as higher HDL concentrations are associated with improved cardiovascular health. Okada LSDRR et al. reported that omega-3 PUFA supplementation elevated HDL levels in patients with metabolic syndrome and NAFLD, corroborating the current study's findings. This lipid-modulating effect of omega-3 PUFAs might further lower the cardiovascular risk in MASLD patients.[16] While there were significant improvements in several parameters, the changes observed in total cholesterol (TC) and low-density lipoprotein (LDL) weren't. This finding corresponds to earlier research, for example, Musazadeh V et al: they have found the modest modulating effects of n-3 PUFAs on TC and LDL levels. Such 'insensitivity' of the measures to change may have been associated with the specific dose and period of treatment with omega-3 as well as individual patient factors.[17-19]

Liver Enzymes

There was a marked decrease in the levels of both ALT ($p<0.05$) and AST ($p<0.05$) associated with omega-3 PUFA supplementation. These enzymes are typically raised in conditions related to liver injury, and a fall in their levels indicates an improvement in hepatic inflammation. These findings have been validated from a systematic review and meta-analysis that aver that there are significant reductions in the levels of ALT and AST in patients with NAFLD due to omega-3 PUFA interventions.[20] The anti-inflammatory role of omega-3 PUFAs acting through the FFAR4 activation of FFA4 could be beneficial regarding this hepatoprotective action.[20]

Ultrasound of abdomen

Ultrasound assessments in the study reveal a significant reduction in hepatic steatosis among the omega-3 PUFA group. This finding aligns with a systematic review and meta-analysis that reported improvements in liver fat content with omega-3 PUFA supplementation.[21] The mechanisms involve modulation of lipid metabolism, where omega-3 PUFAs decrease de novo lipogenesis and increase fatty acid oxidation, thereby reducing hepatic fat accumulation.[21]

Body Mass Index and Waist Circumference

A significant reduction in BMI was noted among participants receiving omega-3 supplementation. This is further supported by Albracht-Schulte K et al. who found in their study that combining omega-3 PUFA supplementation with a calorie-restricted diet enhanced weight loss as compared to dieting alone. The effect of spirulina on body weight could be related to the control of energy intake and the regulation of appetite functions.[22] The value of BMI found in this study spells out a potential role in the management of body weight thus adding to what is known about omega-3 PUFAs. A study by Salman HB et al. also showed the effectiveness of omega-3 supplementation on weight loss and improved body composition in addition to dieting and exercise, likely through mechanisms of appetite control, and energy expenditure enhancement, although further research will still be needed to clarify these effects.[23]

Fasting Blood Sugar

On assessing omega-3 PUFA supplementation, the study showed a marked reduction in fasting blood sugar levels hence underscoring the possible beneficial role of the intervention in enhancing glycemic control among MASLD patients. These findings are supported by Chen C et al. and He XX et al., who in their studies related the reduction in FBS levels to improved insulin sensitivity and anti-inflammatory effects. Omega-3 PUFAs reduce gluconeogenesis and increase hepatic triacylglycerol oxidation, thus enhancing glucose tolerance. These findings advocate the use of omega-3 PUFAs as an accompanying mode of therapy for an ameliorated glycemic profile in MASLD.[24,25]

CONCLUSION

Omega-3 PUFA supplementation represents a significant improvement in liver health among MASLD patients by decreasing triglycerides, liver enzymes (ALT and AST), and hepatic fat accumulation (ultrasound findings) as well as improving BMI and HDL cholesterol. There is also a decrease in fasting blood sugar. Nevertheless, the changes in total cholesterol, LDL, and waist circumference did not show considerable improvement.

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