Effects of PUFA on lipid level in patients with diabetes: Hospital based study

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ABSTRACT
Introduction: Diabetes mellitus is a metabolic disease that is associated with dyslipidemia; manifested by high levels of triglyceride, LDL and low HDL which increase the risk of cardiovascular disease. This study investigates the effect of polyunsaturated fat (PUFA) on the glycemic state and the lipid profile of diabetic patients.
Material and Methods: A 3 months observational study of 63 type 2 diabetic patients, divided the patients in to PUFA group n. =31 given Omacor (omega-3) 1capsule /day as a source of n-3 PUFA and control group n. = 32 continued on their routine anti-diabetic medication. Subjects took their routine diet and usual diabetic medication. Fasting blood glucose and lipid profile of the two groups were assessed pre and post enrolment in the study.
Results: 3 months of n-3 PUFA consumption lowered the levels of fasting blood glucose, triglycerides, total cholesterol, and LDL in diabetic patients with an increase in HDL level. Although n-3 PUFA improved the lipid profile and the blood glucose level in type 2 diabetic patients yet were of no statistical significance when compared to the initial values of the patients or with the diabetic group who did not have n-3 PUFA.
Conclusion: 3 months n-3 PUFA supplementation for type 2 diabetes decreases fasting blood glucose, total cholesterol, triglyceride, LDL with an increase in HDL level. Non-statistical significant findings suggest that a longer term clinical trials and /or large sample size are required to conclusively establish the effect of n-3 PUFA on cardiovascular risk, lipid profile and outcomes in type 2 diabetic patients.

Key words: blood glucose level, diabetics, lipid profile, polyunsaturated fats (PUFA)

INTRODUCTION AND OBJECTIVES

Diabetes mellitus is a general metabolic disorder of all -the three - energy nutrients. It is a potentially preventable public health problem with a worldwide prevalence rate of 8.9% - 12.3%, the number of diabetic patients is estimated to increase from 117 million in 2000 to 366 million in 2030[1,2,3]. Atherosclerotic cardiovascular disease is the most common problem encountered in diabetes[4], which is associated with typical dyslipidaemia[5]. Postprandial lipoproteins abnormal metabolism in type 2 diabetes is atherogenic[6,7,8 9] and it increases CAD Coronary artery disease (*CAD*) morbidity in type 2 diabetes. Since, postprandial lipemia determines plasma HDL concentrations[10]; the negative correlation between HDL and CAD seems to originate in highly positive correlation between postprandial triglyceride concentrations and CAD[11]. Diabetic patients with moderate hypertriglyceridemia are at increased risk for coronary heart disease (CHD)[12].

Physical activity and dietary intervention have been recommended to control and prevent diabetes and *hypertriglyceridemia*[13,14], severely elevated triglycerides levels should be treated with lipid-lowering drugs[15].

Epidemiologic studies conducted on populations taking high intakes of fish had less risk of cardiovascular disease and diabetes, suggesting that (n-3) fatty acids play a role in controlling, preventing diabetes[14], giving a protective effect against atherosclerotic disease and

reducing serum triglycerides levels[16]. Fatty acids are fundamental components of phospholipids in cell membranes so by altering the fatty acid composition of membrane phospholipids, (n-3) fatty acids modify membrane mediated processes such as insulin transduction signals, activity of lipases, and synthesis of eicosanoids. It also controls the expression of various metabolic genes (e.g. genes involved in lipid and glucose metabolism and adipogenesis) in part through the activation of PPAR[14,15,16].

Our literature review suggests an overall small, yet useful role of omega-3 PUFAs in improving the glycemic state and lipid profile of type 2 diabetic patients. Due to the presence of contradictory findings and results in previous studies depending on the specific populations' strata, and study design, we could not establish a strong recommendation regarding the role of PUFAs dietary supplement preparations in the treatment plans of diabetic patient regularly seen in GMC nor could we determine whether such approach is more useful with specific gender, age group or patients with particular co-morbidity such as dyslipidemia and hypertension. We conducted a prospective observational study that has an intervention group and a control group to investigate the effect of omega-3 polyunsaturated fat (PUFA) regular intake on the glycemic state and lipid profile of the type 2 diabetic patients seen at the outpatient department in GMCH .

MATERIALS AND METHODS

Study settings and population

This study was conducted among diabetic patients visiting OPD of internal medicine department at GMCH & RC, Ajman, UAE during the period of June 2011- March 2013.Patients diagnosed with diabetes and on medication were included in the study, excluding patient presented with cardiovascular, renal, retinal or any other complication of diabetes or taking lipid lowering drugs or hormone replacement therapy (women).

Study design and Data collection

This 3 month observational study was approved by GMU research and ethical committees and was performed in accordance with the ethical standards laid down in the 1974 Declaration of Helsinki.

As a part of patient education program offered by GMCH & RC, all the diabetic patients attending the OPD of internal medicine are being educated by their attending physician about the health benefits of PUFA as a nutritional supplement prescribed. Researches screened all the diabetic patients based on the inclusion and exclusion criteria of the study. A pre designed, validated questionnaire was filled to assure explaining the study purpose and procedures, obtaining official consent and to facilitate data collection which included socio-demographic variables, details of diabetes- age of onset, duration, treatment -drugs, dosage and duration-, complication and history of dyslipidemia. Anonymity of the participants was maintained throughout the study. 63 type 2 diabetic patients of both genders were divided according to their consent and acceptance into PUFA group n=31 given 1 g fish oil (Omacor 1g/day) as a source of n-3 PUFA and Control group n= 32. Subjects were followed up for 3 months and were allowed to take their routine diet and diabetic medication without any alterations. Fasting blood glucose and lipid profile of the two groups were assessed pre and post enrolment in the study. Compliance was monitored by contact with the subjects.

Biochemical analysis

Before and after the intervention; FBG, total cholesterol, LDL, HDL, triglycerides levels were assessed. Serum total cholesterol and triglyceride concentrations were determined by enzymatic colorimetric assay (Technicon Instruments, Ltd., NY,USA), HDL was determined enzymatically in the supernatant after precipitation of other lipoproteins with dextran sulfate-magnesium. LDL was calculated using Friedewald formula.

Data Analysis

Data of subjects who completed the study and had both baseline and final measurements (63 patients) were fed into Excel spread sheet and transferred to PASW 19 version software for statistical analysis. Chi-square test was used to determine the association between the variables. Paired and unpaired t-test was used to compare the variables within the group and between groups. The results were expressed as mean ± SD and a p value < 0.05 was considered to be of statistical significant level.

RESULTS

63 patients (31 PUFA group and 32 Control group) were included in the analysis. Participants' mean age was 53.6 with 73% males and a mean duration of diabetes of 8.6 years. Majority of the participants were Arabs 78%. 17 patients had dyslipidemia, 6 patients in PUFA group versus 8 patients in control group. 22 patients were hypertensive, 10 patients in PUFA group versus 12 patients in control group. There were no statistical significant differences detected between the two groups at the start of the study; table 1.

At the start of the study PUFA group showed fasting blood glucose (FBG), triglyceride, cholesterol, HDL and LDL levels of 126.31±48.141mg/dl, 159.93±113.947mg/dl, 166.63±50.809 mg/dl, 43.83±17.560 mg/dl, 91.70±49.275mg/dl respectively versus 135.34±46.553 mg/dl, 141.27±71.172 mg/dl, 171.79±47.271 mg/dl, 43.65±17.080 mg/dl, and 43.65±17.080 mg/dl of the same in control group. The two groups were comparable at the start of the study as no statistical significant differences were detected between the compared parameters in the two groups; table 2.

Table 3 shows that after 3 month control group showed a decrease in FBG, triglyceride, cholesterol, LDL levels by 6.31 mg/dl (4.6%), 10.65 mg/dl (7.53%), 14.76 mg/dl (8.59%), 14.1 mg/dl (13.80%) respectively with an increase in HDL level by 0.74 mg/dl (1.28%), none of the detected changes showed statistical significant difference compared to its level at the start of the study.

PUFA group showed a reduction in the blood levels of FBG, Triglyceride, cholesterol, LDL by 4.4.mg/dl (3.48%), 31.8 mg/dl (19.8%), 9.98 mg/dl (5.89%), 5.04 mg/dl (5.4%) respectively with an increase in HDL level by 1.71 mg/dl (3.9%), the reduction in triglyceride level was the only parameter showing statistical significant difference compared to its level at the start of the study.

Although both groups showed decrease in FBG, triglyceride, cholesterol, LDL and an increase in HDL levels at the end of the study, yet reduction in FBG and cholesterol levels detected in PUFA group were less than what was seen in control group by 1.12% and 2.61% respectively. While the reduction in triglyceride level and the increase in HDL level detected were more in PUFA group compared to control

Table 1: The characteristics of the groups at the starting of the study

Variables	Groups	Control group (32 patients) N (%)	PUFA group (31patients) N (%)	P value
Gender	Male (73%)	24 (75%)	22 (71%)	> 0.05
	Female (27%)	8 (25%)	9 (29%)	> 0.05
Ethnicity	Arabs (78%)	24 (75%)	25 (81%)	> 0.05
	Non Arabs (22%)	8 (25%)	6 (20%)	> 0.05
Patients with dyslipidemia	17 (26.9%)	8 (25%)	9 (29%)	> 0.05
Patients with hypertension	22 (34.9%)	12 (35%)	10 (32%)	> 0.05

Table 2: Blood glucose level and lipid profiles of the study participants at the start of the study

Test	Control group (32 patients)	PUFA group (31patients)	P value
	Mean ±SD (mg/dl)	Mean ±SD (mg/dl)	> 0.05
FBG	135.34±46.553	126.31±48.141	> 0.05
TG	141.27±71.172	159.93±113.947	> 0.05
T.Ch	171.79±47.271	166.63±50.809	> 0.05
HDL	43.65±17.080	43.83±17.560	> 0.05
LDL	102.10±46.117	91.70±49.275	> 0.05

Table 3: Blood glucose level and lipid profiles of the study participants at the end of the study (after 3 months interval)

Test	Control group (32 patients)		PUFA group (31patients)			Mean difference in PUFA group compared to the control group	% difference between the effect seen in PUFA group compared to the effect seen control group	p value
	Mean ±SD (mg/dl)	Mean difference (mg/dl) and % of change compared to the base line	Mean ±SD (mg/dl)	Mean difference (mg/dl) and % of change compared to the base line	p value	(mg/dl)	% difference	
FBG	129.03±47.46	-6.31 (- 4.6%)	121.91±49.14	-4.4 (- 3.48%)	> 0.05	-7.12	-1.12 %	> 0.05
TG	130.62±59.77	-10.65 (- 7.53%)	128.13±77.86	-31.8 (-19.8%)	<0.05*	-2.49	12.27%	<0.05*
T.Ch	157.03±34.88	-14.76 (- 8.59%)	156.65±42.44	-9.98 (- 5.98%)	> 0.05	-0.38	-2.61%	> 0.05
HDL	44.39±15.493	0.74 (1.28%)	45.54±15.493	1.71 (3.9%)	> 0.05	1.15	2.62%	> 0.05
LDL	88±37.064	-14.1 (-13.80%)	86.66±31.192	-5.04 (-5.4%)	> 0.05	-1.34	- 8.4%	> 0.05

group by 12.7 % and 2.62% respectively. The reduction in triglyceride level was the only statistical significant difference detected at the end of the study.

DISCUSSION

Type 2 diabetes arises from insulin resistance rather than the lack of insulin production and most strongly associated with obesity. Insulin resistance causes less efficient glucose take up by the cells, resulting in elevated blood glucose concentrations and increase in hepatic gluconeogenesis which further elevates blood glucose overnight. Chronic elevated blood glucose causes glucose-protein adducts, leading to circulatory dysfunction, retinopathy, kidney damage, and inability to fight infections that may result in gangrene in the limbs[17].

Since (n-3) Fatty acid affects diabetes, insulin action and cardiovascular disease have been under study in the past few years, this study tried to investigate the effects of n-3 PUFAs on diabetic patients and to weigh the detected effects and/or benefit from the statistical and clinical point of view. This was done by giving 1g daily /3 months of fish oil as a source of PUFAs (Omacor 1g/day) to diabetic patients and studying the effects of this supplement on their lipid profile and glycemic state as well as comparing the effects detected with the lipid profile and glycemic state of diabetic patients who were not consuming PUFAs.

At the start of this study the two groups were statistically comparable as there

were no statistical significant differences detected between the two groups regarding age, gender and ethnicity; duration of the disease and the prevalence of dyslipidemia (26.9%) and the prevalence of hypertension (34.9%).

3 months consumption of 1g/day of n-3 PUFAs (Omacor tablets) by diabetic patients showed a statistical insignificant reduction in fasting blood glucose level, in accordance to a study founded that diabetics patients had 16% statistically significant reduction in their fasting blood glucose level after taking 30 ml of olive oil daily/4 weeks[20]. Studies showed that PUFAs increased membrane fluidity, number of insulin receptors and insulin binding, thus decreasing the fasting blood glucose level[13,15].

This study showed that triglyceride level of diabetic patient taking 1g PUFAs daily / 3 months had a statistically significant reduction, matching the findings in diabetic patients consuming 30 ml daily/ 4 weeks of olive oil that had 32% reduction of their triglyceride level[19,21].

Randomized controlled trials studying fish oil supplementation given to diabetic patients showed a statistical significant reduction in triglyceride level specially when recruited hypertriglyceridemic subjects[22]. Omega-3 fatty acids lower triglycerides level by increasing lipoprotein lipase activity and chylomicron clearance[21,23].

This study showed that 1g daily of n-3 PUFAS/3months decreased cholesterol level of the diabetic patients, similar to Puiggros et al.[24] who reported 8.4% significant decrease in total cholesterol level with olive oil-enriched diet [23].

In this study 1g of PUFAs daily /3 months in diabetic patients showed increase in HDL level and decrease in LDL, in accordance to a study that found that 30 ml daily/4 weeks supplementation of olive oil in the diet of diabetic patients increased HLD level by 27% and decreased LDL level by 22% [20]also Rodríguez- Villar showed that high olive oil diet given to type 2 diabetics lowered VLDL-cholesterol by 35% and VLDL-triglyceride by 16% [23]. Lopez-Miranda[24] pointed out that Mediterranean diet, increases HDL-cholesterol plasma levels, and decreases the susceptibility of LDL to oxidation and lipid peroxidation[25].

The effects of n-3 fatty acids on HDL cholesterol and its subfractions are unclear. Studies have demonstrated that HDL- cholesterol subfractions change in composition and absolute size upon n-3 fatty acid treatment: HDL2 level tends to rise compared with HDL3 level [25, 26] and that increase in HDL2/HDL3 ratio may reduce cardiovascular risk[27].

N-3 fatty acids decrease LDL cholesterol by promoting production of triglycerides poor VLDL cholesterol and accelerating conversion of VLDL cholesterol to LDL cholesterol. However, this mechanism remains unclear[28]. N-3 PUFAs decrease LDL level and its susceptibility to oxidation[29].

This study shows that 1g daily/3months n-3 PUFA supplement (Omacor 1g /day) improved lipid profile in type 2 diabetic patients ; manifested by decreasing the levels of triglyceride, cholesterol, LDL with an increase in HLD level . Participants also experienced reductions in fasting blood glucose level although the only statistical significant findings was the reduction in the triglyceride level yet the findings were in accordance to a study that found the positive effect of daily consumption of 30 ml of olive oil as a source of n-3 PUFAS was much more profound in the diabetic group as levels of FBG, TG, T.Ch and LDL decreased by 16-32% compared to normal individuals[20].

Clinical studies reviewed the effect of (n-3) fatty acids on the treatment of both type 1 and 2 diabetes found that using low-dose (<3 g/d) (n-3) fatty acids for 2–24 weeks showed that no effect was found on (FBG) and Triglycerides were decreased in most cases. Total cholesterol was decreased in 6 cases and increased in only 1 case. HDL increased in 4 cases and decreased in 1 case. LDL increased in 5 cases and decreased in 4 cases. Using

high-dose (>3 g/d) studies for 3–24 wks. showed that (FBG) decreased in 3 studies and was not modified in 4 studies. Total cholesterol was not modified. Triglycerides decreased in 6 cases and LDL increased in 6 cases. HDL decreased in 1 case and increased in 2 cases[30].

In summary, in this study n-3 fatty acids have decreased triglycerides level in type 2 diabetic patients and have not shown statistical significant reduction in (FBG) that may imply to its role to restore insulin activity in diabetic patients. The findings of the study suggest that (n-3) fatty acid dosage used maybe relatively low [<3 g (n-3) fatty acids/d] and background diets may have not been controlled. These factors considered as limitations of this study with the lack of and difficulty in performing studies on insulin sensitivity.

Therefore, long-term, large sample size studies on (n-3) fatty acids need to be performed to answer the fundamental question of whether (n-3) fatty acids have beneficial effects on glycemic control and lipid profile of type 2 diabetic patients.

CONCLUSION

3 months supplementation of n-3 PUFA to diabetic patients decreases FBG, total cholesterol, triglyceride, LDL and increases HDL level. Non-statistical significant findings suggests that a longer term , large sample size, high dose studies on (n-3) fatty acids are required to conclusively establish the effect of n-3 PUFA on glycemic control , lipid profile and outcomes in type 2 diabetic patients.

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