ARTICLE

Effects of Simvastatin and Omega 3-fatty Acids on Blood Pressure, Plasma Lipid Profiles, Liver and Renal Function in Type 2 Diabetes

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Abstract
A group of patients with and hyperlipidemia were divided into male and female groups and further subdivided into 3 groups. These groups received, either simvastatin (20 mg daily), Omega3-fatty acid (2g/day), or both. The blood pressure and lipid profile were measured before and after 4 weeks of treatment. Our data showed that treatment with simvastatin did not produce significant effect on blood pressure, however the blood pressure was significantly reduced in patients received omega 3-fatty acid or simvastatin plus omega3-fatty acid. The total cholesterol (TC), triglycerides (TG), and low density lipoprotein (LDL) significantly decreased in all treated groups. The high density lipoprotein (HDL) significantly increased in all treated groups except in the group of males receiving simvastatin. Alanine transaminase (ALT) increased significantly in female and male groups receiving simvastatin, but significantly decreased in same groups receiving omega 3-fatty acid and in the males receiving simvastatin plus omega3-fatty acid. The aspartate transaminase (AST) levels significantly decreased in all treated groups except in the female group given omega3-fatty acid. The alkaline phosphatase (ALP) significantly increased only in the groups given simvastatin alone. The levels of urea and creatinine were not affected in all groups. In our prospective study we found that simvastatin decreased TC, TG and LDL, and resulted in elevation of liver transaminases. Omega3- fatty acid alone or in combination with simvastatin has similar effect on lipid profile and it significantly reduces blood pressure without affecting liver or renal function.

Key words: Type 2 diabetes mellitus, Simvastatin, Omega-3 fatty acid, ALT, AST, ALP , Blood pressure

Introduction

Several studies indicated that Omega-3 fatty acids improve dyslipidaemia (1-3) and their effect may extend to lowering

blood pressure in hypertensive patients (2,3), and reduce the risk of sudden cardiac death (3,4). Therefore the intake of omega-3 fatty acids may be of particular benefit to type 2 diabeted mellitus (T2DM) patients (1,5).

Statins are used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. Statins have been found to prevent cardiovascular disease events in individuals with and without diabetes (6,7) and they are generally safe and well tolerated (7). Although statins are efficacious in patients with T2DM, rates of cardiovascular events remain elevated in such patients even following treatment with statins Omega3-fatty acids which are a group of poly unsaturated fats found in a wide variety of foods (8,9).

The aim of this study is to investigate the influence of simvastatin or omega 3-fatty acid separately and of their combination on blood pressure and lipid profile in Libyan patients with T2DM.

Patients and methods

Study design

This study is a single center prospective study that was conducted at Benghazi Diabetic Center (BDC). The study was approved by the research ethics committee, Faculty of Medicine, University of Benghazi. Newly diagnosed T2DM patients were included in the study. A total of 108 (54 female) newly diagnosed T2DM patients were included in the study. Diagnosis of diabetes mellitus was based on ADA and/or WHO criteria (glycated hemoglobin ≥7%) (10,11). All patients had hyperlipidaemia. Absence of concomitant disease was confirmed by history prior to inclusion. All the patients were on oral hypoglycemic combination therapy (glimeperide plus metformin being a very commonly used combination in our practice). Patients were divided into three groups, 1) Simvastatin 20mg group (19 females and 19 males), 2) Omega 3 fatty acid (2g/day) group (19 females and 19 males) and 3) Simvastatin 20mg + omega 3 fatty acid (2 g/day) group (19 females and 19 males).

Data collection

Patients were newly diagnosed T2DM with less than one year duration. The duration of the study was one month, starting from recruitment day (base line), till the second visit. Data collected included: patient`s name, age, gender, weight (kg), height (cm) and date of first visit. All patients were subjected to the following investigations: fasting plasma glucose, 2hr postprandial plasma glucose, glycated hemoglobin (HbA1c%), total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatise (ALP), urea, and creatinine. All these investigations were performed at the biochemistry laboratory of Benghazi Diabetic Center. All patients were reviewed after one month and all investigations were repeated. The blood pressure

Table 1. Systolic and diastolic blood pressure levels in diabetic patients before and after treatment with simvastatin, omega-3 fatty acid, and their combination in female and male diabetic patients separately.

Blood pressure measurement (mmHg)	Treatment					
	Simvastatin (20mg/day)		Omega-3 fatty acid (2g/day)		Combination	
	Pre-	Post-	Pre-	Post-	Pre-	Post-
Females						
Systolic	124± 2	123±2	128±2	114±2*	128±2	116±2*
Diastolic	78±1	80±1	81±1	73±1*	81±2	74±1*
Males						
Systolic	122± 3	125±2	132±3	112±1*	127±3	116±2*
Diastolic	80±1	81±1	82±2	71±1*	83±2	75±1*

Values represent the mean±SEM
*Significantly different from pretreament ($p<0.05$)

was measured twice after rest for 10 minute with a mercury sphygmomanometer.

Analytical methods

The blood glucose level was determined (12,13) using Beckman Glucose Analyzer (12,13). The serum lipids TC, TG, HDL were measured and LDL was calculated as described previously (13-16). Liver functions tests (serum ALT, AST, ALP), renal function (blood urea nitrogen and serum creatinine) were assayed as previously described (17,18).

Statistical analysis

The results were expressed as mean ±standard error of the mean (SEM). The difference between means of pre and post treated groups was analysed by using paired student's t-test. A p-value less than 0.05 was considered statistically significant.

Results

Effects on blood pressure

Data presented in table1 showed systolic and diastolic blood pressure values were not changed in both female and male patients treated with simvastatin alone. However following 4 weeks of treatment with simvastatin, both the systolic and diastolic blood pressures were significantly decreased in the groups of males and females receiving omega-3 fatty acid or combination of simvastatin plus omega-3 fatty acid.

Effect on the lipid profile

The levels of TC, TG, HDL and LDL decreased significantly in the female group receiving simvastatin (Table 2). The levels of TC, TG, and LDL were also significantly lower in the male patients receiving simvastatin but the HDL has not changed significantly. In the female and male patient receiving the omega-3 fatty acid or the combination of omega-3fatty acid and simvastatin the levels of TC, TG, and LDL have significantly decreased however HDL levels have significantly increased.

Effect on liver and renal functions

Markers of liver function (i.e. serum levels of ALT, AST and ALP) significantly increased in both male and female patients treated with simvastatin (Table 3). Serum levels of ALT significantly decreased in the female patients treated with omega-3 fatty acids, but AST and ALP levels did not change significantly. In the female group treated with combination only AST significantly reduced but

Table 2. Effect of simvastatin, Omega-3 fatty acid separately and in combination of simvastatin and Omega-3 fatty acid on the lipid profile in diabetic patients.

Lipid profile	Treatment					
	Simvastatin (20mg/day)		Omega-3 fatty acid (2g/day)		Combination	
	Pre-	Post-	Pre-	Post-	Pre-	Post-
Females:						
TC (mg/dl)	231±5	143±5**	194±7	158±4**	245±9	172±7**
TG (mg/dl)	197±8	139±6**	170±5	120±5**	236±7	117±7**
HDL(mg/dl)	42±1	35±1**	42±1	54±2**	40±1	51±1**
LDL(mg/dl)	150±5	80±5**	118±8	81±4**	157±9	98±6**
Males:						
TC (mg/dl)	203±5	168±6**	184±5	142±5**	212±5	155±3**
TG (mg/dl)	193±12	136±9**	188±4	109±7**	200±7	140±5**
HDL(mg/dl)	39±2	37±1	36±1	46±1**	39±1	44±1*
LDL(mg/dl)	125±4	104±6**	116±10	93±6*	133±5	84±3**

Values represent the mean±SEM.
*Statistically different from pretreatment ($p<0.05$).
**Statistically different from pretreatment ($P<0.01$).

Table 3. Liver function represented by serum levels of the main enzymes ALT, AST and ALP before and after treatment with simvastatin, omega-3 fatty acid, and their combination in female and male diabetic patients separately.

Liver function tests	Treatment					
	Simvastatin (20mg/day)		Omega-3 fatty acid (2g/day)		Combination	
	Pre-	Post-	Pre-	Post-	Pre-	Post-
Female:						
ALT(U/L)	17±1	23±2*	27±1	16±1*	21±2	17±1
AST(U/L)	21±2	28±2*	22±2	20±3	23±2	17±1*
ALP(U/L)	152± 7	172±8*	165±8	170±7	149±5	155±6
Male:						
ALT(U/L)	20±2	27±2**	24±2	17±1*	27±1	14±1**
AST(U/L)	20±2	26±2*	26±1	17±1*	28±1	17±2**
ALP(U/L)	159±6	190±8*	155±5	151±5	163±3	160±4

Values represent the mean±SEM.
*Statistically different from pretreatment ($p<0.05$).
**Statistically different from pretreatment ($P<0.01$).

Table 4. Renal functions represented by serum urea and creatinine levels before and after treatment with simvastatin, omega-3 fatty acid, and their combination in female and male diabetic patients separately.

Renal function tests	Treatment					
	Simvastatin (20mg/day)		Omega-3 fatty acid (2g/day)		Combination	
	Pre-	Post-	Pre-	Post-	Pre-	Post-
Females:						
urea level (mg/dl)	23±2	23±2	21±1	22±2	18±1	19±2
creatinine level (mg/dl)	64±4	66±4	63± 3	60± 3	60±4	62±3
Males:						
urea level (mg/dl)	25±2	24±2	26±3	25±3	25±2	26±2
creatinine level (mg/dl)	78±4	80±3	84±4	80±4	79 ±5	76±5

No significant difference was observed.

ALT and ALP levels were not significantly affected. The levels of ALT, and AST in the male patients treated with simvastatin significantly decreased however ALP level significantly increased in post treated patients as compared to pretreatment. Results in table 3, indicate that the level of ALT and AST significantly decreased in the male groups treated with omega-3 fatty acid or combination of omega-3 fatty acid plus simvastatin, whereas the level of ALP did not change. The blood urea and creatinine in all treated groups showed no significant difference from the base line (Table 4).

Discussion

Statins are used commonly for prevention of cardiovascular events in individuals with and without diabetes (6). Our data show no significant effect of statin on BP after one month of treatment, perhaps related to the short duration of the study. This is at variance with Golomb and colleagues (19) who reported a significant effect on BP after 6 months of daily treatment with a statin. Our data showed that omega-3 fatty acids alone or in combination with simvastatin cause a decrease in both systolic and diastolic blood pressure in diabetic patients of both genders. The suggested mechanism of decrease in BP by omega-3 fatty acids may be due to the decrease of Ca^{++} influx into vascular smooth muscles (20) and also may involve an increased in nitric oxide release (21). **S**imvastatin has a short duration of action, hence it is given at night, to get the maximum effect, because cholesterol synthesis appears to occur mostly at night (22). Several investigators reported that the administration of short acting simvastatin at night produced a reduction in the total cholesterol and LDL (23,24).

Dyslipidemia affects people with type 2 more often than type 1 diabetes. Our data revealed that daily use of simvastatin (20mg) for one month led to a significant reduction in cholesterol level in both male and female patients with diabetes. These findings are in agreement with several studies (25,26). In addition, statins are very effective in reducing the level of LDL (27,28). These studies are supported with our results, in which male and female patients showed significant decrease in the level of LDL after 4 weeks of treatment. The possible mechanism is that the decrease in cholesterol concentration activates a cellular signalling cascade culminating in the activation of sterol regulatory element binding protein, a transcription factor that up-regulates expression of the gene encoding LDL receptor. Increased LDL receptor expression lead to enhanced uptake of plasma LDL, and consequently decreases plasma LDL-cholesterol (30).

The high triglycerides level is an important risk factor for heart disease and also considered as a marker for metabolic syndrome. In the current study, the statin therapy significantly lowered TG levels in agreement with preious reports (30). The suggested mechanism may be related to the inhibition of HMG-CoA reductase, the rate limiting enzyme in cholesterol biosynthesis by statin (31). The resultant reduction in hepatocyte cholesterol concentration triggers increased expression of hepatic LDL receptors, which clear LDL and LDL precursors from the circulation (32) that may inhibit hepatic production of apolipoprotein B-100 and lower the synthesis and secretion of triglyceride-rich lipoproteins (33). Statin therapy has been shown to increase the level of plasma HDL-cholesterol (34). On the other hand a paradoxical decrease in the serum HDL was observed in diabetics who received statin (35). Our results showed a significant reduction in HDL in females but no significant change in males receiving statin. Furthermore, the present study suggests that the omega-3 fatty acid significantly decreases serum cholesterol levels. The suggested mechanism may be due to effects of omega-3 fatty acids on the amount of cholesteryl esters in nascent VLDL which is markedly reduced in the presence of eicosapentaenoic acid (EPA) (36). This might cause a reduction in plasma LDL-cholesterol concentration (37) and this is in accordance with our results in which omega-3 fatty acids significantly lowered LDL levels. It is suggested that the omega-3 fatty acids lower plasma LDL levels by reducing the rate of synthesis of apoprotein B (38).

Omega-3 fatty acids cause elevations in HDL cholesterol (37,39). The results of Harris are supported with our results which showed a significant increase in HDL level in patients treated with omega-3 fatty acids. The increased concentration of HDL cholesterol may be explained by the reduced concentration of free fatty acids in plasma (40-42).

Omega-3 fatty acids appear to have a beneficial effect on the triglyceride level, the omega 3 fatty acid supplementation significantly reduced TG level (43) which is considered as cardioprotective effect, these results are in agreement with the results of our study. The decrease in TG level, probably because omega-3 fatty acids inhibit esterification of other fatty acids in addition to being poor substrates for TG-synthesising enzymes (44). Omega-3 fatty acids may also reduce TG production by increasing fatty acid oxidation via peroxisomal β-oxidation (41).

Co-administration of omega-3 fatty acids with statin in our study showed significant decrease in cholesterol, TG and LDL in both gender whereas HDL levels were significantly elevated in diabetic patients of both genders. The suggested mechanism may be due to increase in LDL particle size and decreased TG level in dyslipidemic patients with type 2 diabetes than in patients receiving statin monotherapy. The therapy was well tolerated without significant adverse effects (45). The combination of omega-3 fatty acids with simvastatin improves lipid profile to greater extent than simvastatin alone due to synergistic effect of combination therapy in which each drug worked by different mechanisms of action.

The most commonly reported hepatic adverse effect of statin is the phenomenon known as transaminitis, in which liver enzyme levels are elevated in the absence of proven hepatotoxicity (46), this is consistent with our results which observed significant increase in ALT, AST and ALP. These adverse effects are usually asymptomatic, reversible, and dose-related (41). In the liver statins inhibition of cholesterol synthesis is much more than in any other tissue, therefore, it is not surprising to observe elevations in the liver enzymes in patients received statins (47). However the omega- 3 fatty acid in our study resulted in significant decreased in liver enzymes ALT, AST and ALP in agreement with the previous reports (48) that showed a decline in transaminase levels in patients with hypertriglyceridemia treated with omega-3 fatty acids. The proposed mechanism may be attributed to the membrane stabilizing action of omega-3 fatty acids on the hepatocytes, suggesting that this substance may act as an antioxidant that makes the hepatocytes less susceptible to the damaging action of noxious agents, as well as its conversion to lipid protective mediators (49). The statin and omega-3 fatty acids when combined showed a significant decrease in liver enzymes. Thus, the hepatotoxic effect of statin may be blunted by omega 3 fatty acids indicating a hepatoprotective effect of omega-3 fatty acids.

In the present study, there was no change in the renal function (urea, creatinine) after 4 weeks of all treatments however, many studies reported the beneficial effect of statin on renal function (50). In the present work, the period of one month may be insufficient and longer time duration may be needed to demonstrate the effect of simvastatin on kidney function. From this study we conclude that, simvastatin is a powerful drug that lowers TC, TG and LDL, and may consequently decrease the risk of cardiovascular disease in diabetic patients, but when used as a single drug it increases the levels of liver enzymes. Omega-3 fatty acids are essential for normal growth and health, and the awareness of their health benefits has dramatically enhanced. This study also demonstrated the efficacy, safety, and good tolerability of omega-3 in the treatment of hyperlipidemia in type 2 diabetic patients without any elevation in liver enzymes (hepatoprotective). Omega-3 fatty acid also decreases, systolic and diastolic BP, so they are safe to be used in obese and hypertensive diabetic patients. Finally, the combined therapy of simvastatin and omega-3 fatty acids may represent the optimal management of diabetic dyslipidaemia to reduce the cardiovascular risk without affecting the liver and renal functions.

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