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Beneficial Effects of Omega-3 Fatty Acids on Low Density Lipoprotein Particle Size in Patients with Type 2 Diabetes Already under Statin Therapy

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Beyond statin therapy for reducing low density lipoprotein cholesterol (LDL-C), additional therapeutic strategies are required to achieve more optimal reduction in cardiovascular risk among diabetic patients with dyslipidemia. To evaluate the effects and the safety of combined treatment with omega-3 fatty acids and statin in dyslipidemic patients with type 2 diabetes, we conducted a randomized, open-label study in Korea. Patients with persistent hypertriglyceridemia (≥200 mg/dL) while taking statin for at least 6 weeks were eligible. Fifty-one patients were randomized to receive either omega-3 fatty acid 4, 2 g, or no drug for 8 weeks while continuing statin therapy. After 8 weeks of treatment, the mean percentage change of low density lipoprotein (LDL) particle size and triglyceride (TG) level was greater in patients who were prescribed 4 g of omega-3 fatty acid with statin than in patients receiving statin monotherapy (2.8%±3.1% vs. 2.3%±3.6%, P=0.024; -41.0%±24.1% vs. -24.2%±31.9%, P= 0.049). Coadministration of omega-3 fatty acids with statin increased LDL particle size and decreased TG level in dyslipidemic patients with type 2 diabetes. The therapy was well tolerated without significant adverse effects.

Keywords: Diabetes mellitus, type 2; Dyslipidemia; Fatty acids, omega-3; Hypertriglyceridemia; Low density lipoprotein particle

INTRODUCTION

It is well recognized that the major cause of mortality in type 2 diabetes is cardiovascular disease (CVD). Dyslipidemia, a common lipid disorder in diabetes, is a major modifiable risk factor of CVD. Diabetic patients have increasingly been recommended to use statins at higher doses. However, despite the effort to reduce low density lipoprotein cholesterol (LDL-C) with statins, cardiovascular events continue to occur in two-thirds of all patients [1]. This suggests that additional therapeutic strategies are required to achieve more optimal reduction in cardiovascular risk among diabetic patients with dyslipidemia.

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Recently, triglyceride (TG) has emerged as an important therapeutic target for residual risk reduction of CVD [2].

The major focus of this study was to assess the beneficial effects of omega-3 fatty acids on LDL particle size and lipid profile by adding omega-3 fatty acids in patients with type 2 diabetes who were already under statin therapy. Omacor, a purified formulation of omega-3 fatty acid (1 g containing 465 mg of eicosapentanoic acid and 375 mg of docosahexanoic acid; Gun-il Pharmacy, Seoul, Korea) known as a TG-lowering agent [3], was used in this study.

METHODS

This randomized, open-label, multicenter, parallel groups, phase IV study was carried out across four centers in Korea. Eligible subjects included adults (aged 18 to 80 years) with type 2 diabetes and mixed dyslipidemia. Patients with persistently high fasting TG level (>200 mg/dL) and LDL-C level (>100 mg/dL) despite a minimum of 6 months of statin therapy (simvastatin, pravastatin, atorvastatin, pitavastatin, rosuvastatin) were diagnosed as mixed dyslipidemia (week -6, screening visit). They were instructed to discontinue other lipid-altering supplements except statin and to maintain current statin therapy. Patients with persistent hypertriglyceridemia were also included from the pool of dyslipidemic patients (week 0, 2nd visit). They were randomly assigned to three groups: O3FA4S group, 4 g of omega-3 fatty acid and statin; O3FA2S group, 2 g of omega-3 fatty acid and statin; and the control group, statin monotherapy. The doses of previous statin were not changed for the remainder of the study. Subjects were followed-up at week 4 and week 8.

The primary efficacy endpoint was the mean percentage change in LDL particle size across 8 weeks in three study groups. The secondary efficacy endpoints included the percent changes in other lipid parameters (total cholesterol [TC], TG, high density lipoprotein cholesterol [HDL-C], LDL-C), apolipoprotein (apo) A1, and apo B. Safety profile was assessed by monitoring adverse events, measuring vital sign and checking blood tests. Noncompliance (less than 80%) was assessed by counting returned capsules.

All blood samples were taken after an overnight fast. Hematologic testing and biochemical testing (blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, total bilirubin, albumin, alkaline phosphatase, glucose, glycated hemoglobin [HbA1c]) were assessed. We measured serum TC and TG using Hitachi 7,600 Autoanalyzer (Hitachi Ltd., Tokyo, Japan), HDL-C and LDL-C using direct enzymatic methods, and apo A1 and apo B level using turbidometry (Roche, Basel, Switzerland). Measurement of LDL particle size was conducted by using continuous disc polyacrylamide gel electrophoresis. Statistical analyses were performed using SAS version 9.13 (SAS Institute Inc., Cary, NC, USA). The standard threshold of $P<0.05$ was used to define a significant result.

RESULTS

Baseline characteristics

Forty-nine patients were included in this study (17 in O3FA4S group, 15 in O3FA2S group, and 17 in control group). The baseline characteristics were similar among the groups. The mean age of study participants was 56 years, and mean body mass index was 25.7 kg/m^2.

Lipid profiles and efficacy

There were no significant difference in the initial (week 0) lipid profiles among the three groups. After 8 weeks of treatment, as shown in Table 1 and Fig. 1, mean LDL particle size increased in all groups, and the percentage change was significantly greater in patients taking 4 g of omega-3 fatty acid with statin than in patients receiving statin monotherapy (2.8%±3.1% vs. 2.3%±3.6%, $P=0.024$). Significant reduction in TG level was shown after 8-week treatment in all groups. The percentage change from baseline TG level was significantly greater in O3FA4S group than in the control group (-41.0%±24.1% vs. -24.2%±31.9%, $P=0.049$). TC level was significantly reduced at 8 weeks from baseline only in O3FA4S group (-0.44%±0.66 mg/dL, $P=0.018$), but the percentage change was not significantly different compared to the control group. In all groups, neither HDL-C nor LDL-C level showed any significant change during the study period. There were no significant differences between O3FA2S group and the control group after 8 weeks of respective treatment.

Safety and compliance

The mean HbA1c level increased after 8-week treatment in O3FA4S group (at screening, 7.01%±0.87%; at week 8, 7.27%±1.08%; $P=0.043$) without a significant increase in fasting glucose level. However, no significant differences were observed in changes of HbA1c levels between three groups. The combination of omega-3 fatty acid and statin had no notable

Table 1. Changes from baseline to week 8 in efficacy parameters

Parameter	O3FA4S (n=17)	O3FA2S (n=15)	Statin (n=17)
LDL particle size, Å			
Baseline	258.4±7.9	258.0±6.4	255.7±8.3
Week 8	265.5±4.1	262.1±9.0	261.3±5.8
Difference	7.1±7.6[a]	5.4±7.5[b]	5.7±8.9[b]
% Change	2.8±3.1[c]	2.1±3.0	2.3±3.6
TC, mg/dL			
Baseline	161.8±24.1	161.9±21.0	170.6±23.4
Week 8	146.1±28.4	152.5±21.3	157.5±29.4
Difference	-16.8±25.3[b]	-9.4±24.7	-11.6±21.9
% Change	-9.6±14.4	-5.0±13.0	-6.6±13.4
TG, mg/dL			
Baseline	295.7±81.9	283.7±68.2	321.5±139.3
Week 8	171.7±73.4	174.3±95.4	244.2±136.8
Difference	-124.0±84.2[a]	-109.5±108.2[a]	-77.4±92.7[a]
% Change	-41.0±24.1[c]	-37.0±30.0	-24.2±31.9
HDL-C, mg/dL			
Baseline	38.8±7.8	41.9±8.9	41.9±12.1
Week 8	39.0±9.7	45.8±13.4	41.5±10.8
Difference	0.15±7.8	3.9±7.5b	-0.44±6.6
% Change	1.2±17.3	8.7±14.9	0.4±17.1
LDL-C, mg/dL			
Baseline	82.5±17.1	75.4±17.6	82.0±30.3
Week 8	73.8±21.9	72.0±18.9	77.2±17.6
Difference	-8.7±22.6	-3.4±14.6	-5.63±20.2
% Change	-9.6±24.0	-3.0±18.7	-3.0±35.6
Apo A1, g/L			
Baseline	142.0±19.9	149.9±19.3	144.1±29.4
Week 8	134.0±21.9	155.4±18.4	142.4±26.3
Difference	-8.1±21.4	5.5±9.1[b]	-1.7±17.3
% Change	-4.9±13.7	3.9±5.9	-0.2±12.9
Apo B, g/L			
Baseline	82.2±16.9	82.5±13.8	87.5±15.7
Week 8	80.1±21.4	77.1±19.1	83.2±19.5
Difference	-1.9±14.7	-5.5±12.1	-4.32±18.3
% Change	-1.9±18.0	-6.9±14.9	-4.3±19.3

Values are presented as mean±standard deviation. Using paired *t*-test or Wilcoxon signed rank test.
O3FA4S group, 4 g of omega-3 fatty acid and statin; O3FA2S group, 2 g of omega-3 fatty acid and statin; statin group, statin monotherapy; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; Apo A1, apolipoprotein A1; Apo B, apolipoprotein B.
[a]Intragroup difference, $P<0.01$, [b]Intragroup difference (at baseline and at week 8), $P<0.05$, [c]O3FA4S vs. statin, $P<0.05$.

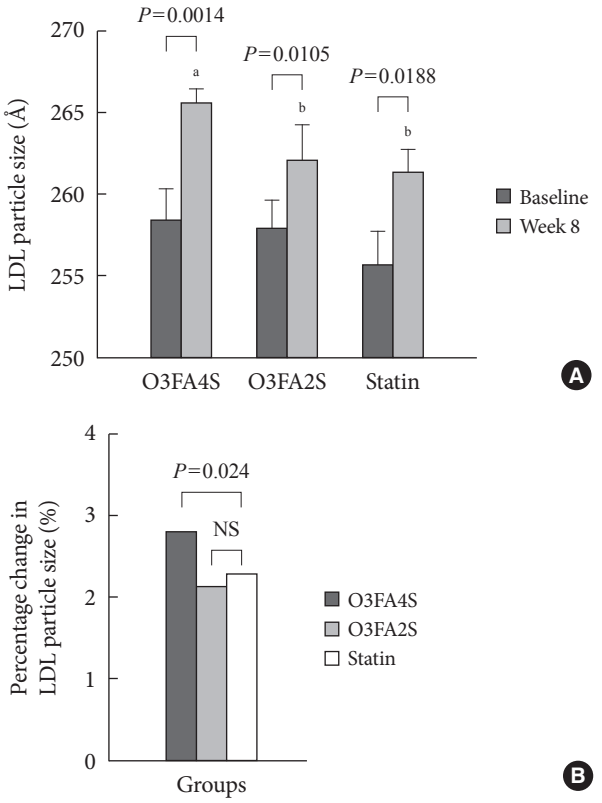

Fig. 1. (A) Mean low density lipoprotein (LDL) particle size at baseline and at week 8, using Wilcoxon signed rank test (for O3FA4S and O3FA2S group) or paired *t*-test (for statin only group). (B) Mean percentage changes in LDL particle size from baseline to week 8, using analysis of covariance. O3FA4S group, 4 g of omega-3 fatty acid and statin; O3FA2S group, 2 g of omega-3 fatty acid and statin; Statin group, statin monotherapy; NS, not significant. [a]$P<0.01$, [b]$P<0.05$.

effect on liver function, renal function, blood cell count, systolic and diastolic blood pressure, pulse rate, or body temperature. There was no significant difference among the three groups in the proportion of patients experiencing adverse events (five participants in O3FA4S group, two in statin group, $P=0.056$). All were temporary mild complaints, such as diarrhea, dyspepsia, peripheral edema, insomnia, and flushing. The estimated compliances for omega-3 fatty acid of two groups were similar regardless of dosage (92.5% in O3FA4S group and 92.6% in O3FA2S group).

DISCUSSION

The distinguishing features of diabetic dyslipidemia from other usual dyslipidemia include elevated TG, presence of small,

dense LDL-C particles, and decreased HDL-C [4] with relatively normal LDL-C [5]. The American Diabetes Association has determined a separate non-HDL-C target goal for diabetic patients (130 mg/dL) regardless of presence of overt CVD [6], reflecting the importance of non-HDL-C reduction in addition to lowering LDL-C.

The TG-lowering effects of omega-3 fatty acid are well known, which is reflected in this study. Our result is not inferior to the percentage change in TG level reported by a study using 20 mg of rosuvastatin monotherapy and fenofibrate 135 mg add-on therapy (-26.9% vs. -42.6%) [7].

However, whether omega-3 fatty acid has beneficial properties on LDL particle remains controversial [8-11]. This study showed that adding supplement of omega-3 fatty acid 4 g/day to statin therapy significantly increased LDL particle size compared to statin monotherapy alone. Recently, Boizel et al. [12] observed that TG/HDL-C ratio was significantly reduced after combined treatment with omega-3 fatty acid and fluvastatin in diabetic patients, suggesting the transformation of small dense LDL to larger particles. As omega-3 fatty acid supplementation was found to accelerate chylomicron TG clearance by increasing the expression of hepatic lipoprotein lipase [13] and reducing intestinal lipoprotein production in rodent model [14], further detailed studies observing the effects of omega-3 fatty acids on lipoprotein subfraction will be needed.

In summary, despite the limitations of this study, including small sample size and short treatment duration, this study results implies that combination therapy of omega-3 fatty acids and statin could result in a significant additional benefit in terms of LDL particle size and TG level in dyslipidemic patients with type 2 diabetes. Coadministration of omega-3 fatty acid 4 g with statin was well tolerated without significant adverse events. Further studies characterizing the potential cardiovascular benefit of coadministration of omega-3 fatty acids with statin in diabetic dyslipidemia are needed.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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