Efficacy and Safety of Da-Chai-Hu-Tang in Lipid Profile in High-Risk, Statin-Treated Patients with Residual HyperTG: An 12-Week, Randomized, Active-Control, Open Clinical Study

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Research

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Abstract

Introduction:

Da-chai-hu-tang (DCHT) is one of the insurance-covered herbal extracts, which proved the effect on reducing serum triglycerides (TG) and Low-density lipoprotein (LDL) cholesterol levels in animal experiment and small clinical trials. The aim of this study was to evaluate the efficacy and safety of DCHT in high-risk, statin-treated patients with residual hypertriglyceridemia.

Methods

This was a 12-week, randomized, active-controlled, open-label, investigator-initiated, single center trial. A total of 50 patients were screened. After a 2-week run-in period, 42 of these patients with high cardiovascular risks whose LDL cholesterol levels were controlled by statin treatment, but TG levels of 200 to 500mg/dL were randomly assigned 1:1 to the OMEGA3 (1000mg twice a day) group or DCHT (1 pack (3g) three times a day) group for 12 weeks. The primary endpoint was defined as the percentage change of TG at 12 weeks compared to the baseline, and changes in other lipid profiles and endothelial cell function by reactive hyperemic index (RHI) were included as secondary endpoints. Safety analyses were also performed.

Results

The baseline characteristics were similar in both groups. In the OMEGA3 group, the average TG level decreased from 294.4 (71.9) to 209.9 (107.8) mg/dL ($p = 0.004$), and in the DCHT group, from 288.7 (59.0) to 227.5 (98.0) mg/dL ($p = 0.001$). The percentage change of TG was − 27.5 and − 22.4 ($p = 0.575$), respectively, and there was no significant difference between the both groups. LDL cholesterol in the OMEGA3 group decreased from 88.6 (21.7) to 80.8 (17.5) mg/dL ($p = 0.049$), and from 86.1 (21.5) to 82.8 (15.4) mg/dL ($p = 0.406$) in the DCHT group. The difference was not significant. RHI also showed no significant change at the baseline and end of treatment, from 1.588 to 1.764 in the OMEGA3 group and from 1.901 to 1.858 in the DCHT group. There were no severe adverse events in both groups, and at 12 weeks, there was one patient in each group whose LFT increased more than twice compared to baseline.

Conclusions

In high-risk, statin-treated patients with residual hypertriglyceridemia, administration of OMEGA3 or DCHT for 12 weeks showed a significant reduction in TG, and the effect of DCHT was not inferior to OMEGA3.

Trial registration:

The study protocol was approved by the Ethics Review Board of Kyung Hee University Hospital (KHUH 2019-07-035-003), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

1. Background

Dyslipidemia is a major risk factor for well-known cardiovascular diseases (CVD), especially LDL cholesterol.[1] However, previous studies showed that residual cardiovascular risks persist in patients with optimal LDL cholesterol levels, and other lipid indicators such as triglycerides (TG), non-HDL, and remnant cholesterol have emerged.[2–6]

Hypertriglyceridemia (hyperTG) is known as an independent risk factor for coronary artery disease (CAD).[7–11] OMEGA3 fatty acid is a drug that has proven to reduce triglyceride in patients with hyperTG known through several RCTs for its effectiveness and safety in single-dose or combination with statin treatments.[12] Also, a comparison of icosapent ethyl and placebo, identified significant reductions in ischemic events, including cardiovascular death.[13] However, there are no treatments for hyperTG, which have been found to reduce cardiovascular disease cases in double blind, randomized studies conducted on patients who are already undergoing statin treatment.[14,15] Therefore, further study will be needed on other drugs that are effective for hyperTG.[16]

There are several studies on effects of herbal drugs for dyslipidemia, and Da-chai-hu-tang (DCHT) is one of insurance-covered herbal extracts on the market. DCHT identified to inhibit hepatic triglyceride biosynthesis in HepG2 human hepatocytes.[17] Also, the effect of DCHT has also been demonstrated improvements of lipid profiles in animal experiments. In hyperlipidemia animal models induced by high-fat diet, a combined administration of statin and DCHT for 18 weeks showed a decrease in total cholesterol, liver fat contents, and size of adiopocytes compared to the statin-only treated group.[18–21] In addition, DCHT showed reduction of lipid profiles in hyperlipidemia patients.[22]

To the best of our knowledge, no study investigated the effectiveness and safety of DCHT compared to OMEGA3 in statin treated patients. Thus, we designed this study to compare DCHT and OMEGA3 regard to lipid profiles improvement for the statin treated patients at high risk of cardiovascular disease.

2. Methods

2.1. Patients

Adults aged ≥ 19 years with hyperTG (levels greater than 200 mg/dL and less than 500 mg/dL) and with optimal LDL cholesterol levels within target range through statin treatment at least for 2 months were initially screened.[23] In addition, patients diagnosed with cardiovascular disease (CVD), diabetes mellitus, peripheral artery disease, or abdominal aneurysms, or with high cardiovascular risks were enrolled in this trial. The exclusion criteria are as follows: History of an allergic reaction in trial drugs, history of acute

coronary syndromes, cerebrovascular disorders, interventional or surgical coronary revascularization within 12 weeks, diagnosed with malignant tumors in the past 5 years, uncontrolled high blood pressure, uncontrolled diabetes, abnormal liver, renal or thyroid function tests. Those who took drugs that may affect lipid profiles within 8 weeks prior before participating in the trial were also excluded. Written informed consent was obtained from all patients, and the Ethics Review Board of Kyung Hee University Hospital approved this study (KHUH 2019-07-035-003).

2.2. Study design

The trial was a 12-week, randomized, active-controlled, open-label, investigator-initiated, single center trial. Since this was a therapeutic exploratory clinical trial without prior clinical studies, we set the sample size to 50 patients. A total of 50 patients were screened from February, 2020 to April, 2021, in Kyung-Hee Medical Center, and 42 patients with high cardiovascular risks whose LDL cholesterol levels were stable by statin treatment, but TG levels of 200 to 500mg/dL were randomly assigned 1:1 to the OMEGA3 group or DCHT group after a 2-week run-in period. Patients received OMEGA3 1000mg twice a day or DCHT 1 pack (3g) three times a day for 12 weeks. The flow chart of clinical trial is presented in Fig. 1.

2.3. Study medication

DSHT extract was produced by Hanpoong Pharmaceutical Company (Seoul, Republic of Korea) and comprised the following eight herbs: Bupleuri radix, Pinelliae tuber, Zingiberis rhizoma recens, Scutellariae radix, Paeoniae Radix, Zizyphi Fructus, Ponciri Fructus Immaturus, and Rhei Radix et Rhizoma. The estimated herbs with 10 times the volume of water were mixed and incubated at 90–100°C for 4 h for extraction. After filtering the extract, the filtrate was sprayed and freeze-dried to obtain 3 g dried extract. OMEGA3 was used 1gram capsule of OMACOR® produced by Kunil Pharmaceutical Company (Seoul, Republic of Korea).

2.4. Efficacy and Safety Assessment

The primary efficacy endpoint was the percentage change in triglyceride from baseline to the end of the treatment. The secondary efficacy endpoints included the percentage changes in other lipid profiles, such as non-HDL-C, total cholesterol, LDL-C, HDL-C, Apo A-I, Apo B, Remnant cholesterol at 12th week from the baseline. In addition, changes in endothelial cell function were included as secondary endpoints. Lipid parameter samples were measured by the laboratories of each hospital using standard procedures. Endothelial cell function was evaluated by reactive hyperemic index (RHI) using an Endo-PAT 2000 device. Peripheral arterial tone signal is measured from patient's fingertip by recording finger arterial pulsatile volume changes. Results of 15-minute tests are recorded and RHI score is generated which represents endothelial cell function.

Safety analyses were also performed by monitoring of adverse events, vital signs, laboratory tests including liver and renal function tests, thyroid function test, glycated hemoglobin, urinalysis. Adverse events were defined as occurred, worsened, or became serious during the study period. The causal relationship between the study drug and adverse events was evaluated.

2.5. Statistical analysis

Continuous variables were expressed as mean (SD) and compared using the 2-sample t test. Categorical variables were expressed as frequencies and percentages, and the Chi-square test was used for comparison. Two-sided $p < 0.05$ was considered statistically significant. The differences of percent changes in lipid parameters and changes in endothelial cell function tests between OMEGA3 and DCHT groups were compared using the student t-test or Mann-Whitney U test according to normal distribution. The safety assessment variables were analyzed using t-test or the Wilcoxon rank sum test, and the differences of frequencies were compared using Chi-square test and Fisher's Exact test. All analyses were performed using SPSS version 22K (SPSS Korea Inc.).

3. Results

3.1. Baseline characteristics

Baseline characteristics are summarized in Table 1. The mean age was 63.7 years, and the patient population was predominantly men (69.0%). Demographics were generally balanced between treatment groups. Also, there was no significant difference in patients' past medical history and smoking history between two groups. The mean baseline TG level was 294.4 mg/dL in OMEGA3 group and 288.7 mg/dL in DCHT group, with no significant difference. There were no significant differences in baseline total cholesterol, LDL, HDL, Apo A-1, non-HDL, remnant cholesterol, and RHI, but the mean ApoB level was slightly higher in OMEGA3 group, respectively ($p = 0.018$).(Table 2)

Table 1
Baseline characteristics

	OMEGA3 (n = 20)	DCHT (n = 22)	*p* value
Age	62.5 ± 8.6	64.9 ± 8.2	0.36
Gender			0.43
Female	5 (25.0)	8 (36.4)	
Male	15 (75.0)	14 (63.6)	
BMI	26.6 ± 3.5	26.9 ± 2.7	0.74
Past medical history			
Stable angina	5 (25.0)	9 (40.9)	0.28
ACS	8 (40.0)	7 (31.8)	0.58
PCI	11 (55.0)	8 (36.4)	0.23
Stroke	2 (10.0)	2 (9.1)	1.00
Carotid atherosclerosis	5 (25.0)	2 (9.1)	0.23
DM	12 (60.0)	11 (50.0)	0.26
HTN	14 (70.0)	18 (81.8)	0.48
Current smoker	3 (15.0)	2 (9.1)	0.34

BMI; Body mass index, ACS; Acute coronary syndrome, PCI; Percutaneous Coronary Intervention, DM; Diabetes Mellitus, HTN; Hypertension, Data represent the number, frequency, or means ± SD

Table 2
Changes in lipid profiles before and after the treatment

	OMEGA3			DCHT			
	Baseline	12 weeks	Percent change (%)	Baseline	12 weeks	Percent change (%)	*p* value
TG	294.5 ± 72.0	210.0 ± 107.8	-27.6 ± 33.6	288.7 ± 59.1	227.5 ± 98.1	-22.5 ± 24.1	0.58
Total cholesterol	151.2 ± 30.8	142.6 ± 26.8	-4.6 ± 14.8	152.2 ± 27.1	146.6 ± 20.0	-2.1 ± 14.2	0.59
LDL-C	88.6 ± 21.8	80.8 ± 17.5	-6.8 ± 16.2	86.2 ± 21.5	82.9 ± 15.4	2.7 ± 40.4	0.49
HDL-C	42.7 ± 8.5	44.2 ± 10.8	3.7 ± 14.5	45.4 ± 8.1	46.7 ± 8.1	4.1 ± 16.0	0.93
Apo A-1	126.9 ± 71.8	128.1 ± 24.9	0.8 ± 10.4	132.8 ± 15.0	133.9 ± 14.9	1.4 ± 10.5	0.86
Apo B	79.5 ± 17.5	74.9 ± 16.5	-4.5 ± 15.8	75.8 ± 12.4	74.6 ± 11.9	-0.8 ± 12.8	0.41
non-HDL	108.5 ± 30.3	98.0 ± 26.1	-7.5 ± 18.1	106.8 ± 25.5	99.9 ± 20.9	-3.8 ± 20.7	0.54
LDL-C/HDL-C	2.1 ± 0.7	1.9 ± 0.6	-9.0 ± 16.7	1.9 ± 0.5	1.8 ± 0.5	1.4 ± 46.9	0.62
TC/HDL-C	3.6 ± 1.0	3.4 ± 1.0	-6.7 ± 16.6	3.4 ± 0.7	3.2 ± 0.7	-4.1 ± 19.1	0.65
Non-HDL-C/HDL-C	2.6 ± 1.0	2.4 ± 1.0	-9.1 ± 21.9	2.4 ± 0.7	2.2 ± 0.7	-4.8 ± 28.2	0.59
Apo B/Apo A-I	0.6 ± 0.2	0.6 ± 0.2	-4.9 ± 15.0	0.6 ± 0.1	0.6 ± 0.7	-1.3 ± 16.1	0.46
Remnant cholesterol	19.9 ± 10.8	17.2 ± 11.2	4.3 ± 83.4	20.64 ± 9.2	17.00 ± 8.3	3.2 ± 82.1	0.72

TG, total glyceridel; LDL-C, Low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; Apo A-1, Apolipoprotein A1; Apo B, Apolipoprotein B; non –HDL, non-high-density lipoprotein cholesterol; TC, total cholesterol

3.2. Efficacy analyses

In the OMEGA3 group, the average level of TG decreased from 294.5 mg/dL to 210.0 mg/dL and LDL level reduced from 88.6 mg/dL to 80.8 mg/dL during the 12-week period. These differences were found to be statistically significant ($p = 0.004$, $p = 0.049$). LDL/HDL cholesterol was also significantly reduced ($p = 0.020$), but increase in HDL cholesterol was not statistically significant ($p = 0.294$). There was no significant difference in other lipid parameters, total cholesterol, Apo B, non HDL, TC/HDL, non-HDL, Apo

B/Apo A-1, remnant cholesterol and endothelial cell function indicator. The mean TG level in the DCHT group showed a significant decrease from 288.7 mg/dL to 227.5 mg/dL ($p = 0.001$). The other lipid profiles showed no significant change. (Table 2) The endothelial cell function, measured with RHI, was the secondary end point of our study, varying from 1.588 to 1.754 in the OMEGA3 group and from 1.901 to 1.858 in the DCHT group. There was no significant difference in RHI change between both groups. ($p = 0.094$, $p = 0.821$, respectively.)

Table 2 showed the percentage changes in triglycerides and other lipid parameters at the end of treatment. The percent change of triglycerides, which was the primary efficacy endpoint in this study, was found to be -27.6% in the OMEGA3 group and − 22.5% in the DCHT group with no significant difference ($p = 0.575$). However, there were no significant differences in the percent change of other lipid profiles, the secondary outcomes.

3.3. Safety analyses

During the study, trial treatments were well tolerated. In the OMEGA3 group, baseline AST, ALT, and Creatinine level were 33.1U/L, 33.1U/L, and 0.9mg/dL and there were no significant differences of 34.2U/L, 34.5U/L, and 0.9mg/dL at the end of the treatment, respectively. In the DCHT group similarly changed AST, ALT and Cr from 32.1U/L, 35.2U/L, 0.8mg/dL to 34.5U/L, 35.3U/L and 0.8mg/dL with no statistically significant differences.

One patient in OMEGA3 group and two patients in DCHT group had adverse events and reported adverse events were generally mild. The patient in OMEGA3 group had subclinical hypothyroidism, which did not require treatment. One of patients in DCHT group had a 3.6-fold increase in ALT level compared to baseline, and the other patient showed microscopic hematuria in urinalysis. There was no significant difference in the incidence of adverse events between the treatment groups. None of the reported adverse reactions were thought to had a causal relationship to the trial drug.

4. Discussion

To the best of our knowledge, it is the first study to evaluate the efficacy on the lipid profiles of DCHT compared to OMEGA3 treatment. Our study found that administration of DCHT for 12 weeks leads to significant reduction in TG level in patients with hyperTG and optimal LDL cholesterol level by statin treatment. There is no significant difference of efficacy between OMEGA3 and DCHT treatments. In addition, there were no other significant changes in other lipid profiles and endothelial cell function.

DCHT is a combination of various natural products for controlling hyperlipidemia. The main components are made up of belows; Bupleurum root, Pinellia tuber, Scutellaria root, Peony root, Rhebarb and Poncirus trifoliate.[21] It could be explained that the effect of DCHT performed by the pharmacological action of Rhubarb.[24,25] The Rhubarb inhibits pancreatic lipase, reducing fat absorption within the gastrointestinal tract.[24,25] Previous studies have shown that administration of rhubarb improves dyslipidemia by inhibits Acyl-CoA cholesterol acetyltransferase and increases the expression of cholesterol 7-hydroxylase. These

actions lead to increase of fecal bile acid secretion and lower bile acid pool in gallbladder.[26,27] Poncirus trifoliate, is another component of DCHT, may reduce TG and LDL cholesterol and increase HDL cholesterol through inhibition of fatty acid synthase (FAS), stearoyl-CoA desaturase 1 (SCD1) and increase of carnitine palmitoyl transferase 1a (CPT1a), insulin receptor substrate 2 (IRS2) in the liver. It also inhibits lipoprotein lipase (LPL) through regulation of CCAAT-enhancer-binding protein (C/EBPβ) in the adipocyte.[28] Beta-sitosterol, induced from Pinellia tuber and Scutellaria root, reduces the absorption of cholesterol in gastrointestinal tract and increases expression of LDL receptor mRNA in hepatocyte.[21,29] Based on pharmacological actions of the components of DCHT and previous studies above, it is expected that DCHT would improve lipid levels in patients with dyslipidemia. In particular, it is believed that the adding of DCHT in statin-treated patients could further increase its effectiveness through expression of LDL receptors.

A significant decrease in LDL levels was confirmed in the OMEGA3 group, while no significant changes were seen in the DCHT group for other lipid profiles, including LDL cholesterol. In the DCHT group, the average level of LDL was 86.18 mg/dL at baseline and 82.86 mg/dL at the end of treatment. The percent change of LDL was 2.70%. These results may have been due to differences in life style of patients including diet, or lack of the cumulative dose of DCHT.

RHI measured by EndoPAT 2000 showed no significant change in both groups. Previous studies confirmed the effectiveness of OMEGA3 on vascular endothelial function showed conflicting results depending on the type or total amount of prescribed OMEGA3 and the target patient group.[30–33] Based on previous studies, the total cumulative dose of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) over 95g is known to improve endothelial dysfunction, even before significantly decreasing triglyceride levels.[34] However, in diabetic patients, there was no significant improvement in endothelial cells.[32] The result of our study is considered to be due to the inclusion of 12 (60.0%) and 11 (50.0%), respectively, in OMEGA3 and DCHT groups. Therefore, it is too early to conclude that DCHT is ineffective in improving endothelial cell function, and further research will be needed.

Safety issue is important concern in lipid lowering agents. Data showed that no serious adverse events occurred in both groups. None of three patients who had side effects complained of any specific symptom, and the lab results improved without any treatment. Considering these results, the dosing of DCHT is thought to be relatively safe. It is also believed that DCHT could be practically used in real world, as the benefits of additional TG reduction in statin treated patients with high cardiovascular risk.

This study have some limitations. Firstly, this study did not perform the double-blind study. Since the effect of OMEGA3 on hyperTG is already established, we concluded it is reasonable to design the trial as an active control group, open label study. Secondly, it has relatively small number of sample size. In addition, long-term follow-up observations would be also required to confirm that improvements in dyslipidemia lead to a reduction in CVD. Further study should be perform the double-blinded study later in order to minimize the bias caused by an open trial.

5. Conclusion

In conclusion, in high-risk, statin-treated patients with residual hyperTG, administration of OMEGA3 or DCHT for 12 weeks showed a significant reduction in TG, and the effect of DCHT was not inferior to OMEGA3.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the local ethics committee, the Ethics Review Board of Kyung Hee University Hospital (KHUH 2019-07-035-003). All involved participants signed written informed consent forms before enrollment.

Consent for publication

Not applicable.

Availability of data and materials

They are available from the corresponding authors upon reasonable request.

Competing interests

The authors declare no competing interests.

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None.

Authors' contributions

Not applicable.

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Figures

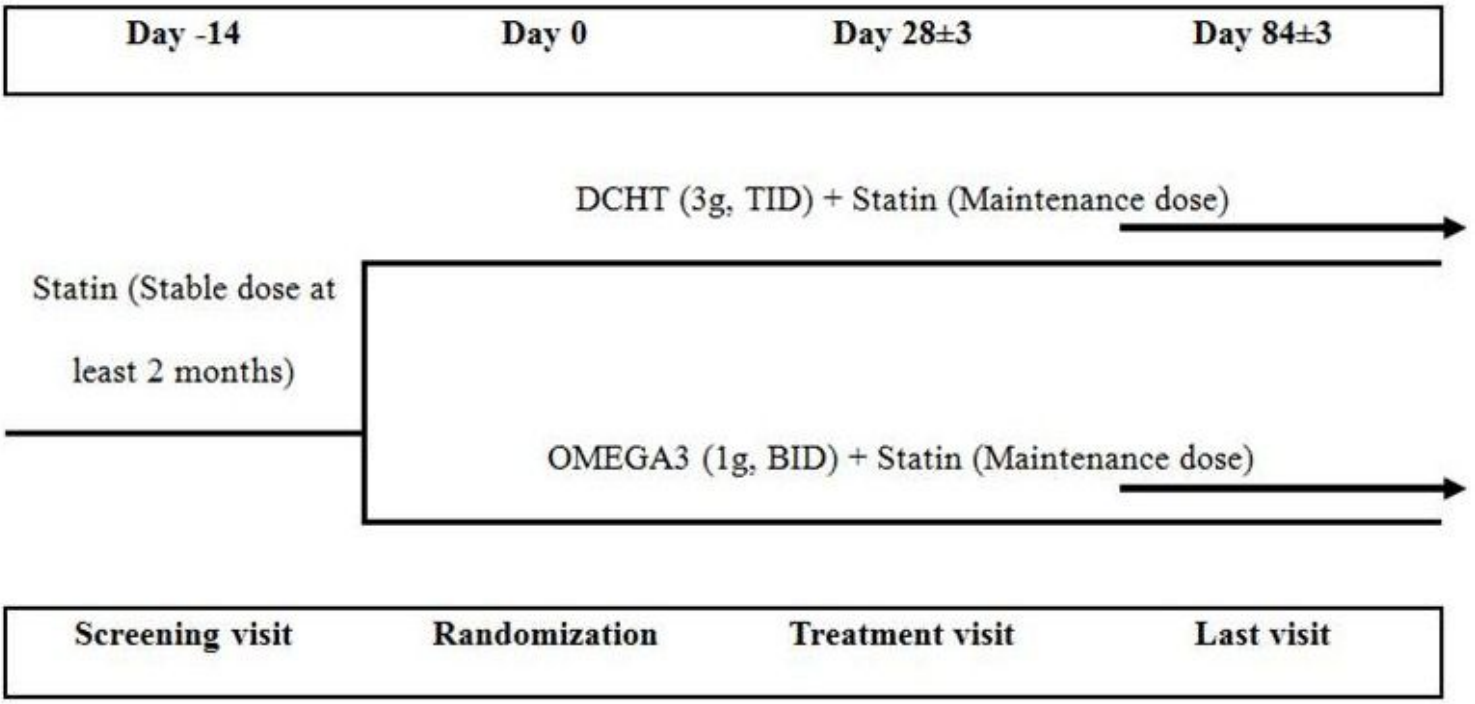

Figure 1

The flow chart of clinical trial

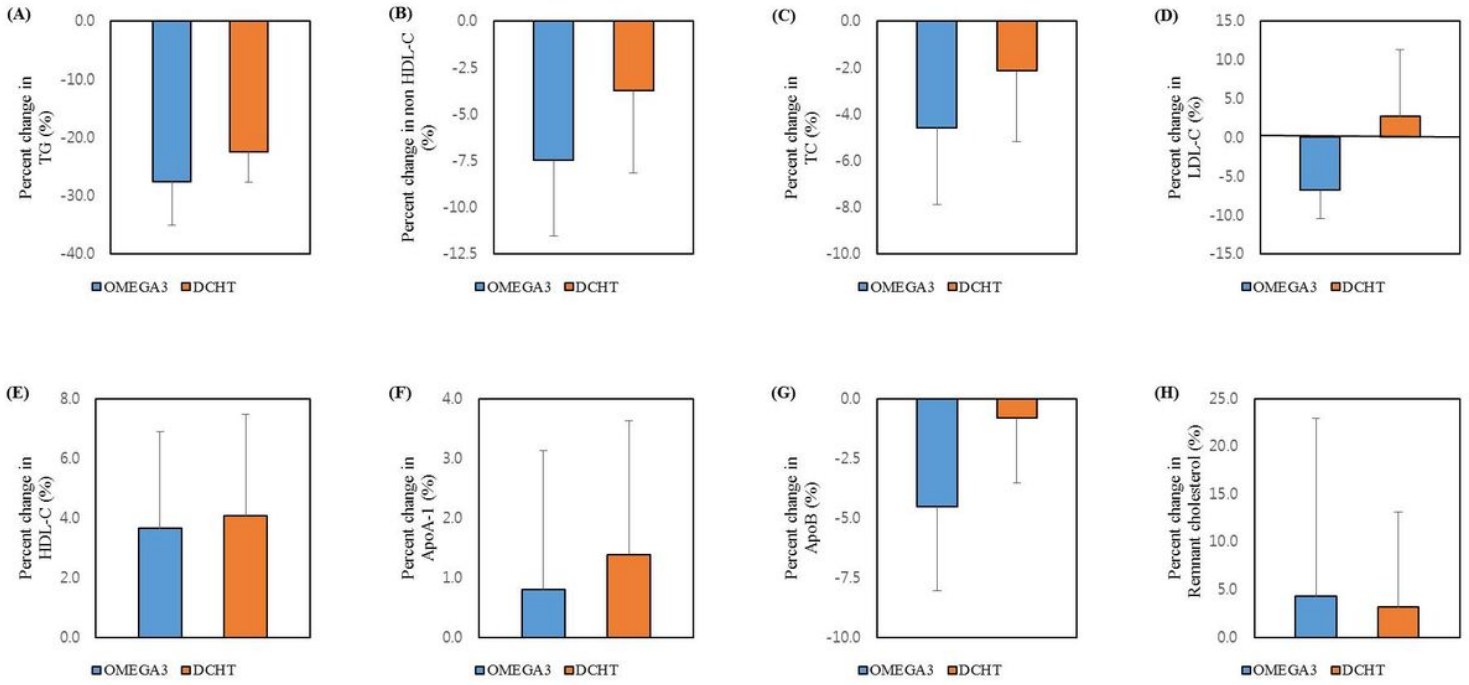

Figure 2

Percent changes in lipid profiles (%), (A) Triglyceride, (B) non-high-density lipoprotein cholesterol, (C) Total cholesterol, (D) Low-density lipoprotein cholesterol, (E) High-density lipoprotein cholesterol, (F) Apolipoprotein A1, (G) Apolipoprotein B, and (H) Remnant cholesterol. Data are expressed as the percent change (%) ± standard error of the mean (SEM).