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Effects of the Switching From High-Purity Eicosapentaenoic Acid to Combination of Eicosapentaenoic Acid and Docosahexaenoic Acid on Metabolic Parameters: A Retrospective Longitudinal Study

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Abstract

Background: Effects of the switching from high-purity eicosapentaenoic acid ester (hp-EPA) to n-3 fatty acid formulation containing EPA and docosahexaenoic acid (DHA) on metabolic parameters remain largely unknown.

Methods: We retrospectively picked up patients who had been prescribed EPA + DHA for 2 months or longer after the prescription of hp-EPA for 2 months or longer between January 2010 and December 2015. We compared the data at baseline and at 2 months after the switching from hp-EPA to EPA + DHA.

Results: Thirty-six patients were eligible for the analyses in our study. Serum triglyceride (TG) showed a non-significant decrease by approximately 9% after the switching. Serum TG showed a non-significant decrease by 24% and 10%, in the switching to the formulation including half daily dose of EPA and DHA and the formulation including the same daily dose of EPA and DHA, respectively. In patients who had shown a decrease in TG after the switching, serum TG at baseline was higher than that in patients who had shown an increase and non-change in TG after the switching. Further, in patients who had shown a decrease in TG after the switching to the formulation including the same daily dose of EPA and DHA, serum TG was significantly higher than that in patients who had shown an increase and non-change in TG. In the analysis of all patients, in patients with baseline TG ≥ 150 mg/dL, TG tended to decrease. In the analysis of patients who underwent the switching to the formulation including the same daily dose of EPA and DHA, in patients with baseline TG ≥ 150 mg/dL, TG significantly decreased.

Conclusion: We studied effects of the switching from hp-EPA to EPA + DHA on metabolic parameters, and found that the switching is more effective to reduce TG in patients with higher TG levels at baseline.

Keywords: Coronary risk factors; Docosahexaenoic acid; Eicosapentaenoic acid; Triglyceride

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Introduction

n-3 polyunsaturated fatty acids (FAs) have been reported to be effective in reducing the risk of cardiovascular diseases [1-3]. In Japan, compared with a modest fish intake of once a week and/or 20 g/day, a higher intake was associated with reduced risk of coronary heart disease among middle-aged persons, indicating an effectiveness of fish oil including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for prevention of coronary heart disease [4]. We previously reviewed the articles about effects of fish oils intake on high-density lipoprotein (HDL) metabolism, and concluded that fish oils consumption, especially DHA consumption, may be favorably associated with HDL metabolism [5]. Further, we reviewed the articles about effects of intake of fish or fish oils on the development of diabetes, and concluded marine n-3 polyunsaturated FAs have beneficial effects on the prevention of type 2 diabetes in Asian populations [6]. Accumulated data have suggested that n-3 FA prevents cardiovascular diseases and improves coronary risk factors. However, it remains unknown which FA improves coronary risk factors more, EPA or DHA. High-purity EPA ester (hp-EPA) and n-3 FA formulation containing 465 mg of EPA and 375 mg of DHA per gram (EPA + DHA) have been approved and widely used to date in Japan. Here, we studied effects of the switching from hp-EPA to EPA + DHA on metabolic parameters.

Materials and Methods

Subjects

This study was approval by the Institutional Ethics Committee in National Center for Global Health and Medicine (NCGM-G-001909-00), and was also performed in accordance with the Declaration of Helsinki.

Table 1. Baseline Characteristics of the Study Subjects (n = 36)

Age (years)	63.8 ± 16.4
Sex (male/female)	21/15
Body height (cm)	160.4 ± 9.8
Body weight (kg)	66.2 ± 14.9
Body mass index (BMI) (kg/m^2)	26.3 ± 5.4
Patients taking anti-diabetic drugs (n)	14
Patients taking anti-hypertensive drugs (n)	19
Patients taking anti-platelet agents (n)	9
Patients taking lipid modifying agents (n)	35
Statins	17
Ion-exchange resin	2
Fibrates	4
Ezetimibe	12

We selected patients who had been prescribed EPA + DHA for 2 months or longer after prescription of hp-EPA for 2 months or longer between January 2010 and December 2015, based on medical charts. We compared the data at baseline and at 2 months after the switching from hp-EPA to EPA + DHA. Body weight, HbA1c, serum total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), non-HDL-C, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured almost at the same time point at the baseline and at 2 months after the switching.

Comparison of the variables determined before and after was analyzed by a paired Student's *t*-test. All data were expressed as mean ± SD. $P < 0.05$ and $P < 0.01$ were considered to be statistically significant and have a tendency, respectively.

Results

We found 526 and 130 patients who had taken hp-EPA and EPA + DHA at least once between January 2010 and December 2015, respectively. Fifty-eight patients had taken both hp-EPA and EPA + DHA, and 36 patients had undergone the switching from hp-EPA to EPA + DHA.

Table 2. Changes in Daily EPA Dose by the Switching From High-Purity EPA to EPA + DHA

Daily EPA dose before switching (mg/day)	Daily EPA dose after switching (mg/day)	n
600	930	1
600	1,860	1
900	930	4
1,200	930	1
1,800	930	8
1,800	1,860	17
2,700	930	2
2,700	1,860	1

Table 1 shows the baseline characteristics of the studied subjects. Table 2 shows the changes in daily EPA dose by the switching from hp-EPA to EPA + DHA. Table 3 shows effects of the switching from hp-EPA to EPA + DHA on metabolic parameters. Body weight, TC, HDL-C, LDL-C, non-HDL-C, AST, ALT and HbA1c almost did not change. TG showed a non-significant decrease by approximately 9% after the switching.

We divided patients into two subgroups: patients underwent the switching from hp-EPA (1,800 mg/day) to EPA (930 mg/day) + DHA (750 mg/day) which is the switching to the formulation including half dose of EPA and DHA (half EPA + DHA) (n = 8) and patients underwent the switching from EPA (900 and 1,800 mg/day) to EPA (930 and 1,860 mg/day) + DHA (750 and 1,500 mg/day) which is the switching to the formulation including the same daily dose of EPA and DHA (same EPA + DHA) (n = 21). In both groups, metabolic parameters except for TG almost did not change (Tables 4 and 5). Serum TG showed a non-significant decrease by 24% and 10% in the switching to the half EPA + DHA and the same EPA + DHA, respectively.

Comparison of serum TG at baseline in subgroups which were divided by effect of the switching from hp-EPA to EPA + DHA on serum TG was shown in Table 6. In patients who

Table 3. Effect of the Switching From High-Purity EPA to EPA + DHA on Metabolic Parameters in All Subjects (n = 36)

	n	Before	2 months after	P value
Body weight (kg)	17	66.2 ± 16.7	66.6 ± 17.1	0.73
Total cholesterol (mg/dL)	26	192 ± 36	192 ± 38	0.77
HDL-cholesterol (mg/dL)	32	48 ± 14	49 ± 15	0.78
LDL-cholesterol (mg/dL)	21	108 ± 36	109 ± 33	0.68
Triglyceride (mg/dL)	34	180 ± 136	163 ± 102	0.23
Non-HDL-cholesterol (mg/dL)	24	138 ± 29	141 ± 36	0.87
AST (IU/L)	34	27 ± 17	28 ± 14	0.34
ALT (IU/L)	32	31 ± 21	32 ± 22	0.35
HbA1c (%)	29	6.4 ± 0.8	6.4 ± 0.7	0.22

Table 4. Effect of the Switching From High-Purity EPA (1,800 mg/day) to EPA (930 mg/day) + DHA (750 mg/day), the Switching to the Formulation Including Half Daily Dose of EPA and DHA, on Metabolic Parameters (n = 8)

	n	Before	2 months after	P value
Body weight (kg)	2	57.5 ± 6.5	57.9 ± 7.2	0.69
Total cholesterol (mg/dL)	6	199 ± 23	198 ± 31	0.87
HDL-cholesterol (mg/dL)	6	52 ± 10	53 ± 10	0.80
LDL-cholesterol (mg/dL)	6	118 ± 43	120 ± 45	0.85
Triglyceride (mg/dL)	7	191 ± 196	146 ± 101	0.41
Non-HDL-cholesterol (mg/dL)	5	142 ± 29	148 ± 41	0.73
AST (IU/L)	7	30 ± 27	34 ± 30	0.53
ALT (IU/L)	7	36 ± 30	34 ± 30	0.47
HbA1c (%)	4	6.2 ± 0.5	6.2 ± 0.5	0.49

Table 5. Effect of the Switching From High-Purity EPA (900 and 1,800 mg/day) to EPA (930 and 1,860 mg/day) + DHA (750 and 1,500 mg/day), the Switching to the Formulation Including the Same Daily Dose of EPA and DHA, on Metabolic Parameters (n = 21)

	n	Before	2 months after	P value
Body weight (kg)	12	57.5 ± 6.5	57.9 ± 7.2	0.69
Total cholesterol (mg/dL)	15	199 ± 23	198 ± 31	0.87
HDL-cholesterol (mg/dL)	15	52 ± 10	53 ± 10	0.80
LDL-cholesterol (mg/dL)	11	118 ± 43	120 ± 45	0.85
Triglyceride (mg/dL)	22	176 ± 119	159 ± 101	0.22
Non-HDL-cholesterol (mg/dL)	15	142 ± 29	148 ± 41	0.73
AST (IU/L)	21	30 ± 27	34 ± 30	0.53
ALT (IU/L)	21	36 ± 30	34 ± 30	0.47
HbA1c (%)	21	6.2 ± 0.5	6.2 ± 0.5	0.49

had shown a decrease in TG after the switching, serum TG at baseline was higher than that in patients who had shown an increase and non-change in TG after the switching. Further, in patients who had shown a decrease in TG after the switching to the same EPA + DHA, serum TG was significantly higher than that in patients who had shown an increase and non-change in TG after the switching.

Effects of the switching from hp-EPA to EPA + DHA on serum TG in subgroups which were divided by baseline TG (TG ≥ 150 mg/dL or TG < 150 mg/dL) were shown in Table 7. In the analysis of all patients, in patients with baseline TG ≥ 150 mg/dL, TG tended to decrease. In the analysis of patients who underwent the switching to the same EPA + DHA, in patients with baseline TG ≥ 150 mg/dL, TG significantly decreased.

Discussion

n-3 FAs have several beneficial cardiovascular protective properties including TG-reducing ability. In the type IIb hy-

Table 6. Comparison of Serum Triglyceride (TG) at Baseline in Subgroups Which Were Divided by Effect of the Switching From High-Purity EPA to EPA + DHA on Serum TG

	n	TG decreased	TG increased and TG did not change	P value
All patients	34	214 ± 152 (n = 22)	119 ± 51 (n = 12)	0.051
Patients underwent the switching to the formulation including half dose of EPA and DHA (EPA → half EPA + DHA)	8	191 ± 214 (n = 6)	127 ± 42 (n = 2)	0.729
Patients underwent the switching to the formation including the same daily dose of EPA and DHA (EPA → same EPA + DHA)	21	212 ± 129 (n = 14)	103 ± 25 (n = 7)	0.049

Table 7. Effect of the Switching From High-Purity EPA to EPA + DHA on Serum TG in Subgroups Which Were Divided by Baseline TG

	n	Before	2 months after	P value
All patients	34			
TG ≥ 150 mg/dL	14	298 ± 140	249 ± 91	0.096
TG < 150 mg/dL	20	99 ± 24	104 ± 54	0.722
EPA → half EPA + DHA	8			
TG ≥ 150 mg/dL	2	417 ± 248	273 ± 80	0.549
TG < 150 mg/dL	5	101 ± 23	97 ± 54	0.907
EPA → same EPA + DHA	21			
TG ≥ 150 mg/dL	8	297 ± 114	239 ± 107	0.009
TG < 150 mg/dL	13	102 ± 20	110 ± 56	0.673

perlipidemic patients, the fish-oil diet led to decreases in both plasma TC (-27%) and TG (-64%), as compared with the control diet. Very-low-density lipoprotein (VLDL) was remarkably reduced [7]. With fish oil, the type V hyperlipidemic patients had marked decreases in TC and TG levels (-45% and -79%, respectively), and VLDL levels were also lowered [7]. Metabolically controlled trials in which large amounts of fish oil were fed to normal volunteers and hyperlipidemic patients showed that n-3 FAs are effective at lowering plasma TC and TG levels [8]. Although more recent trials using smaller, more practical doses of fish oil supplements have confirmed the TG-reducing effect, however, they have shown little effect on TC levels; hypertriglyceridemic patients have shown increases in LDL-C levels while taking n-3 FA supplements [8]. Discrepancies among fish oil studies regarding the effects of n-3 FA on LDL-C levels exist [8].

In the double-blind, randomized crossover study which investigated the effects of 6-week treatment with n-3 FA esters (4 g/day) on serum lipids [9], n-3 FA induced a modest increase from baseline in LDL-C (3.4%), a significant decrease in VLDL (-18.8%), TG (-18.7%), and a significant increase in HDL-C (3.3%). However, in Japan EPA lipid intervention study (JELIS) which used hp-EPA [10], TC, LDL-C and TG significantly decreased by 19%, 25% and 9%, respectively, and only small increase in HDL-C was observed.

Since hp-EPA and EPA + DHA have been approved and widely used to date in Japan, we studied effects of the switching from hp-EPA to EPA + DHA. TG showed a non-significant decrease by approximately 9% after the switching. Serum TG showed a non-significant decrease by 24% and 10% in the switching to the half EPA + DHA and the same EPA + DHA, respectively. Further, our study demonstrated that the switching from hp-EPA to EPA + DHA is more effective to reduce TG in patients with higher TG levels at baseline.

To our knowledge, the present study is the first to show effects of the switching from hp-EPA to EPA + DHA because countries except for Japan where both hp-EPA and EPA + DHA are available, are very limited. We found a case report showing the switching from EPA + DHA to hp-EPA [11]. In the case, the switching produced a decrease in TC, LDL-C, TG and non-HDL-C, by 34%, 28%, 41% and 44%, respectively, challenging our result. However, in our study, 12 of 34 (35%) patients showed an increase and non-change of TG by the switching from hp-EPA to EPA + DHA, suggesting an importance of accumulation of studied subjects.

Present study has several limitations. First, other hypoglycemic, anti-hypertensive, or lipid lowering agents, food intakes and/or exercise levels may have an influence on the study results. Second, the number of studied subjects was small because of the limited availability. Third, since the study was retrospective and based on medical charts, lack of data might influence the results. A more detailed prospective study is recommended to evaluate the effects of switching from hp-EPA to EPA + DHA on metabolic parameters more validly.

Conclusion

We studied effects of the switching from hp-EPA to EPA + DHA on metabolic parameters, and found that the switching is more effective to reduce TG in patients with higher TG levels at baseline.

Author Contributions

HK, SM and HY designed the research. HK and SM collected data. HK, SM and HY analyzed data, and wrote the paper. All authors read and approved the final paper.

Conflicts of Interest

The authors declare that they have no conflicts of interest concerning this article.

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