The Effects of Long-Term Dietary Therapy on Patients with Hypertriglyceridemia

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Aim: This study aimed to evaluate the effect of diet on serum lipids and to assess the effectiveness of long-term dietary therapy for hypertriglyceridemia.

Methods: Seventy-nine patients (34 males and 45 females) with hypertriglyceridemia were enrolled and underwent dietary counseling for 12 months based on the following three recommendations: (1) reduce carbohydrate intake, (2) increase n-3 polyunsaturated fatty acid (PUFA) intake, and (3) limit alcohol drinking. We examined the effect of dietary therapy for 6 months on serum triglyceride (TG) levels and also compared the effectiveness of dietary and combined drug therapies on preventing arteriosclerotic disease from 7 to 12 months.

Results: We observed that serum TG levels of the patients receiving dietary counseling were decreased compared with baseline at 6 months. Body weight and serum TG levels were decreased, and serum high-density lipoprotein levels were increased in the dietary therapy alone group, whereas BW, body mass index, and abdominal circumference were decreased in the combined drug treatment group compared with baselines at 6 and 12 months. Furthermore, the dietary therapy alone group demonstrated reductions in intake of total energy, carbohydrate, and saturated fatty acids, as well as n-6/n-3 PUFA ratio compared with baselines, but only n-6/n-3 PUFA ratio was decreased in the combined drug treatment group.

Conclusion: This study demonstrated a decrease in serum TG level after 12 months of dietary therapy similar to drug therapy, which suggests that it is an effective treatment for hypertriglyceridemia, and heightened awareness should be made to encourage its use.

The clinical trial registration number: UMIN000028860.

Key words: Hypertriglyceridemia, Dietary therapy, Polyunsaturated fatty acid (PUFA), Guidelines

Introduction

Elevated levels of serum triglyceride (TG) promote formation of atheroma and clot by increasing concentrations of remnant lipoprotein (RLP) and small dense low-density lipoprotein cholesterol (sdLDL), activation of the coagulation and fibrinolysis system, and enhancement in insulin (IRI) resistance, which all promote the development of atherosclerosis. A previous study demonstrated that the prevalence of heart disease increased in a concentration-dependent manner with non-fasting serum TGs, fasting serum TG level was an independent risk factor for coronary artery disease (CAD), and hypertriglyceridemia was associated with CAD in patients undergoing treatment for secondary prevention with strictly controlled LDL cholesterol levels in the guidelines, serum TG level (≥150 mg/dL) is employed as diagnostic criteria for CADs because their onset is increased at this level.

In the development of arteriosclerosis, lifestyle changes, such as diet and exercise, and especially diet therapy are important preventive factors. In 2012, the...
Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases were revised for the first time in 5 years. Moreover, the guidelines indicate that improvement of lifestyle habits should be initiated 3 to 6 months in patients with dyslipidemia before they receive medical treatment. Dietary modifications reduce serum TG level without any risk of side effects. However, it is easier to demonstrate an effect with drug treatments, and physicians recommend dietary therapy less frequently. Furthermore, the availability of dietary therapy in dyslipidemia is not evaluated enough, so there is a need to establish an effective method of dietary therapy based on scientific evidence.

In a meta-analysis regarding dietary carbohydrate, fat intake, and serum fatty acid (FA) levels, it was suggested that isoenergetic replacement of dietary fat containing saturated fatty acid (SFA) with carbohydrates produced an increase in fasting TG level. Additionally, the subjects who drank at least 46.0 g/day of alcohol had higher serum TG levels than those who did not drink or drank less than 46.0 g/day of alcohol in a cross-sectional study of Japanese male office workers. Furthermore, many epidemiological intervention studies demonstrated that increased consumption of n-3 polyunsaturated fatty acids (PUFAs) was effective in lowering TG levels and preventing CADs. Thus, dietary intake appears to be closely related to serum lipid levels, serum FA composition, and vascular endothelial function.

In the guidelines, it is recommended that patients with hypertriglyceridemia should mildly decrease intake of carbohydrates, increase consumption of n-3 PUFAs, and cut back on excessive alcohol intake. In previous reports, it was suggested that the intake of supplements of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) could improve serum FA balance, serum lipid levels, and vascular endothelial function, and could be an effective treatment against CAD. Thus, increasing the intake of fish as a major source of n-3 PUFAs (EPA and DHA) was introduced in dietary counseling in this study.

**Aim**

The aims of this study were to evaluate the effect of dietary modifications on serum lipid level and composition and to assess whether long-term dietary therapy based on the following three recommendations listed in the guidelines could improve serum lipid level and composition in hypertriglyceridemia: (1) mild reduction in intake of carbohydrates; (2) increase consumption of n-3 PUFAs; and (3) limit excessive alcohol drinking.

### Methods

**Subjects**

Seventy-nine patients (34 males and 45 females) with hypertriglyceridemia, who attended the Asai medical clinic, were enrolled in this study. Exclusion criteria included patients who are undergoing treatment for cancer and renal or hepatic dysfunction. Written informed consent was obtained from all of the subjects. This study design was approved by the ethics committee of the University of Shizuoka (No.24-45) and performed in accordance with the principles of the Declaration of Helsinki. The clinical trial registration number is UMIN000028860.

**Study Design**

1. **The Effect of Dietary Counseling for 6 Months on Serum TG Level**

Subjects underwent monthly dietary therapy for 12 months based on the following three recommendations listed in the guidelines for prevention of arteriosclerotic disease: (1) mild reduction in intake of carbohydrates; (2) increase consumption of n-3 PUFAs; and (3) limit excessive alcohol drinking. Fasting blood samples were collected, and body weight and abdominal circumference (AC) were measured at every visit. A dietary survey was conducted every 3 months. Seventy-three subjects (33 males and 40 females) completed the first 6 months of the study period, and the six subjects who dropped out before 6 months were excluded from this analysis. We evaluated alterations in various parameters such as serum lipids and composition, physical measurements, and the estimated nutrient intake in the first 6 months of the study period.

2. **Comparison of Dietary Counseling Alone and Combined Drug Treatment from 7 to 12 Months of the Study Period**

Subjects whose serum TG level reached the target range (<150 mg/dL) at 6 months continued to undergo dietary therapy (dietary counseling alone group, \( n = 12 \)), whereas those who did not were started on drug therapy such as EPA preparation (EPA ethyl ester, \( n = 5 \)) or fibrates (combined drug treatment group, bezafibrate: \( n = 3 \), fenofibrate: \( n = 4 \)). The other 10 subjects whose serum TG level did not reach the target range and who rejected medical therapy at 6 months were excluded from this study. Moreover, 4 subjects who dropped out of the study after 6 months were also excluded. Thus, in the last 6 months of the study period, the dietary therapy alone group included 47 subjects, and the combined drug treatment group included 12 subjects. Alterations in various parameters and the estimated nutrient intake during the study period in both
groups were evaluated.

**Measurements**

Height was measured at first visit, and body weight and AC were measured at every visit. Height and body weight of subjects were measured using TANITA Best-weight BWB-700 (Tokyo, JAPAN). AC was measured around the navel using an anthropometric tape. Body mass index (BMI) was calculated using the following formula: BMI (kg/m²) = weight (kg)/height (m)²

Subjects visited the clinic in the morning after not less than 10 h fast, and fasting blood samples were collected at every visit. Blood samples were assessed by the Health Science Institute, Inc. (Kanagawa, JAPAN). Serum TG, total cholesterol (TC), and high-density lipoprotein cholesterol (HDL) levels were measured monthly. Serum LDL level was estimated by the Friedewald formula when serum TG levels were < 400 mg/dL, whereas when serum TG levels were ≥400 mg/dL, the non-HDL level was considered as the LDL level. Non-HDL level was calculated using the following formula: non-HDL (mg/dL) = TC (mg/dL) - HDL (mg/dL). Serum FA, plasma glucose (PG), IRI, high sensitivity C-reactive protein (hsCRP), and sdLDL levels were evaluated every 6 months. The threshold value for insulin resistance (HOMA-IR) was estimated with the following formula: HOMA-IR = PG (mg/dL) × IRI (µU/mL)/405. LDL/HDL, n-6/n-3 PUFA, and EPA/arachidonic acid (AA) ratios, which are reported as risk factors for the onset and prevention of CADs, were calculated

We evaluated the estimated nutrient intake of subjects using a brief-type self-administered diet history questionnaire (BDHQ) methods, which tracked dietary habits during the previous month and took only 20–30 min to answer.

**Statistical Analysis**

All data are presented as mean ± SD. The normality of the data distribution was examined by the Shapiro–Wilks test. Changes in blood parameters before and after dietary intervention were analyzed using paired Student’s t-test for normally distributed data and the Wilcoxon test for nonparametric analysis. Consecutive changes in physical characteristics and clinical factors were analyzed using a repeated analysis of variance (ANOVA) for normally distributed data and the Friedman test for non-normally distributed data. Tukey's
The estimated dietary nutrients assessed by BDHQ following counseling for 6 months in study subjects.

Wilcoxon tests were used to compare non-normal data. P% En, energy ratio of protein; F% En, energy ratio of fat; C% En, energy ratio of carbohydrate. PFC ratio did not include % energy of alcohol. SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; AA, arachidonic acid; EPA, eicosapentaenoic acid; DHA docosahexaenoic acid.

Values are means ± SD (n=73). P values refer to paired Student’s t-tests performed on mean change after nutritional counseling therapy for 6 months. Wilcoxon tests were used to compare non-normal data. P% En, energy ratio of protein; F% En, energy ratio of fat; C% En, energy ratio of carbohydrate. PFC ratio did not include % energy of alcohol. SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; AA, arachidonic acid; EPA, eicosapentaenoic acid; DHA docosahexaenoic acid.

### Results

1) Effect of Dietary Intervention Via Counseling for 6 Months

The average age, BMI, and serum TG level were 65.6 ± 11.2 years, 25.2 ± 3.5 kg/m², and 229 ± 109 mg/dL, respectively, at baseline. The subjects included 10 patients with diabetes, 21 smokers, and 30 drinkers of alcohol, and 66 subjects took anti-hypertensive drug.

Changes in the characteristics of the subjects are shown in Table 1. Serum TG, RLP, TC, sdLDL, and non-HDL levels and the LDL/HDL ratio of the patients receiving dietary counseling were significantly decreased as compared with baseline levels at the end of the first 6 months. The average reduction in serum
Comparison of Dietary Therapy Alone Group and Combined Drug Treatment Group from 7 to 12 Months of the Study Period

Changes in serum TG levels in both groups are shown in Fig. 1. In the dietary therapy alone group, there were significant reductions in serum TG levels at every month compared with baseline, and the decrease in serum TG levels continued throughout the study period. By contrast, serum TG levels were only reduced in the combined drug treatment group following initiation of drug treatment at 7 months. The rate of decrease in serum TG level from baseline to 6 months was 47.1% in the dietary therapy alone group but only 6.5% in the combined drug treatment group, a difference that was significant (p<0.001, data not shown).

On the other hand, the rate of changes were 27.3% and −40.1% (p<0.001) from 7 to 12 months and −38.8% and −44.6% (p=0.373) from baseline to 12 months in the dietary therapy group and combined drug treatment group, respectively.

Serum lipid level and composition and physical measurements in both groups for the study period are shown in Table 3. Baseline levels of serum TG, RLP, HDL, sdLDL, LDL/HDL ratio, non-HDL, IRI, PG, and TG level was 39.7% at 6 months. Serum HDL level at 6 months was significantly increased compared with baseline. There were no significant differences in serum LDL, PG, and hsCRP levels, as well as EPA/AA and n-6/n-3 PUFA ratios after 6 months of dietary counseling. IRI and HOMA-IR levels at 6 months were significantly increased compared with baselines. There were also significant reductions at 6 months in body weight, BMI, and AC compared with baseline values, whereas there was no significant change in BP levels (data not shown).

The estimated nutrient intakes of subjects during the first 6 months of dietary intervention are shown in Table 2. Compared with baselines, total intakes of energy and carbohydrate in the patients receiving dietary counseling were significantly decreased at 6 months, whereas there was no significant decrease in the carbohydrate/energy ratio. No significant difference was observed in the intake of alcohol. EPA + DHA level and EPA/AA ratio were significantly increased after dietary intervention, whereas the n-6/n-3 PUFA ratio was significantly decreased.
Table 3. Changes in the characteristics of the dietary and combined drug treatment groups from 0-12 months

|                      | Dietary counseling alone group | Combined drug treatment group |
|----------------------|-------------------------------|------------------------------|
|                      | Baseline | 6 month | 12 month | Baseline | 6 month | 12 month |
| Mean ± SD            | Mean ± SD |       | Mean ± SD |       | Mean ± SD |       |
| Age (year)           | 67 ± 10  |       |          | 69 ± 12  |       |          |
| Sex (Male/Female)    | 20/27    |       |          | 7/5      |       |          |
| BW (kg)              | 63.6 ± 12.8 | 60.7 ± 11.9 | <0.001 | 59.8 ± 11.5 | <0.001 | 64.5 ± 7.8 | 62.1 ± 7.3 | <0.001 | 61.2 ± 7.9 | <0.001 |
| BMI (kg/m²)          | 25.1 ± 3.6 | 24.0 ± 3.1 | <0.001 | 23.6 ± 3.0 | <0.001 | 25.8 ± 1.9 | 24.8 ± 2.0 | <0.001 | 24.4 ± 2.3 | <0.001 |
| AC (cm)              | 90.6 ± 7.2 | 86.8 ± 7.3 | <0.001 | 86.2 ± 7.1 | <0.001 | 93.1 ± 6.0 | 89.8 ± 7.2 | 0.020 | 89.1 ± 5.7 | 0.001 |
| TG (mg/dl)           | 207 ± 88  | 101 ± 30 | <0.001 | 120 ± 44  | <0.001 | 254 ± 93*  | 232 ± 84*  |       | 133 ± 36*  | <0.001 |
| RLP (mg/dl)          | 10.1 ± 5.4 | 6.7 ± 2.8 | <0.001 | 7.5 ± 3.6  | <0.001 | 21.4 ± 9.7* | 18.9 ± 6.7* |       | 9.1 ± 3.7  | <0.001 |
| TC (mg/dl)           | 206 ± 29  | 199 ± 26 |       | 196 ± 28  | 0.037 | 215 ± 30  | 199 ± 19  |       | 192 ± 24  | 0.005 |
| LDL (mg/dl)          | 115 ± 31  | 119 ± 25 |       | 113 ± 24  |       | 129 ± 32  | 119 ± 22  |       | 118 ± 19  |       |
| HDL (mg/dl)          | 52 ± 14   | 60 ± 17  | <0.001 | 59 ± 18   | <0.001 | 43 ± 7*   | 42 ± 4*   |       | 47 ± 6*   |       |
| sdLDL (mg/dl)        | 38.3 ± 9.8 | 33.7 ± 10.6 | 0.003 | 33.2 ± 11.7 | 0.001 | 51.0 ± 16.1* | 47.1 ± 11.4* |       | 36.2 ± 10.8 | 0.005 |
| non-HDL (mg/dl)      | 153 ± 29  | 139 ± 24 | <0.001 | 137 ± 25  | <0.001 | 172 ± 29*  | 158 ± 19*  |       | 144 ± 22*  | <0.001 |
| LDL/HDL              | 2.34 ± 0.83 | 2.12 ± 0.68 | 0.002 | 2.09 ± 0.75 | <0.001 | 3.07 ± 0.82* | 2.93 ± 0.73* |       | 2.51 ± 0.44 |       |
| PG (mg/dl)           | 95 ± 12   | 98 ± 18  |       | 96 ± 15   |       | 109 ± 13*  | 107 ± 13*  |       | 106 ± 18  |       |
| IRI (µIU/ml)         | 6.4 ± 3.3 | 7.2 ± 3.9 |       | 6.5 ± 3.1 |       | 9.2 ± 3.9* | 11.3 ± 7.1* |       | 8.7 ± 3.9 |       |
| HOMA-IR              | 1.50 ± 0.85 | 1.81 ± 1.33 |       | 1.56 ± 0.79 |       | 2.55 ± 1.32* | 3.02 ± 1.93* |       | 2.38 ± 1.38* |       |
| hsCRP (mg/dl)        | 0.083 ± 0.092 | 0.106 ± 0.136 |       | 0.092 ± 0.120 |       | 0.125 ± 0.134 | 0.212 ± 0.204 |       | 0.124 ± 0.138 |       |

Values are means ± SD (dietary counseling alone group: n = 47, combined drug treatment group: n = 12). Comparisons of the two groups were performed by repeated measures ANOVA and Tukey’s post-hoc tests, and Friedman’s repeated measures ANOVA was used to analyze non-normal data. #: p < 0.05, *: p < 0.01 vs baseline.

BW, body weight; BMI, body mass index; AC, abdominal circumference; TG, triglyceride; RLP, remnant lipoprotein; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; sdLDL, small dense LDL; PG, plasma glucose; IRI, insulin; hsCRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance.

and HOMA-IR in the dietary therapy alone group were significantly lower compared with those of the combined drug treatment group. In the dietary therapy alone group, body weight, BMI, AC, serum TG, RLP, sdLDL, LDL/HDL ratio, and non-HDL levels were significantly decreased, and serum HDL level was significantly increased at 6 and 12 months compared with baselines. In the combined drug treatment group, there were significant decreases at 6 and 12 months in body weight, BMI, and AC compared with baselines similar to the dietary therapy group. After initiation of medical therapy at 7 months, there were significant reductions in serum TG, RLP, TC, sdLDL, and non-HDL levels compared with baselines at 12 months.

The estimated nutrient intakes in both groups for the entire study period of 12 months are shown in Table 4. In the dietary therapy alone group, intakes of total energy, carbohydrate, and SFA, and n-6/n-3 PUFA ratio showed significant reductions at 6 and 12 months compared with baseline levels. Furthermore, the carbohydrate/energy ratio was significantly decreased at 6 months relative to baseline. The EPA/AA ratio was significantly increased at 6 and 12 months compared with baseline. Intakes of EPA, DHA, and EPA + DHA were significantly increased at only 6 months. In the combined drug treatment group, the n-6/n-3 PUFA ratio was significantly decreased at 6 months compared with baseline, whereas there were no significant differences in the other estimated nutrient intakes.

Serum FA levels in both groups are shown in Table 5. Five subjects who started taking EPA preparation (EPA ethyl ester) from 7 months onward were excluded from this analysis. DHA and n-3 PUFA weight ratios were significantly increased and monounsaturated fatty acid (MUFA) weight ratio was significantly decreased at 6 and 12 months compared with baseline levels in the dietary therapy alone group. The PUFA/SFA ratio was significantly increased, and SFA weight ratio was significantly decreased at 6 and 12 months compared with baselines in both groups. However, there were no significant changes in the EPA/AA and n-6/n-3 PUFA ratios in both groups.

Discussion

We examined the influence of dietary counseling
for 6 months on serum TG level and various parameters, and found that serum TG levels were significantly decreased and serum HDL levels were significantly increased after 6 months of dietary counseling as compared with before the intervention. Moreover, intake of carbohydrates was significantly decreased at 6 months compared with baseline (Table 2). In a previous meta-analysis of clinical trials, it was reported that replacing 5% of energy intake in the form of carbohydrates with SFA, MUFA or PUFA decreased serum TG level and increased serum HDL level. A significant reduction in serum TG level and increase in serum HDL level observed in this study are consistent with the previously reported data. In this study, intake of carbohydrates was decreased by approximately 15%, and intake of DHA and EPA+DHA were significantly increased. Thus, these improvements in diet are considered to have contributed to the reduction in serum TG levels observed in our subjects.

Serum TG levels were significantly decreased in the dietary therapy alone group, whereas there were no significant reductions in the combined drug treatment group.
group during the first 6 months of the study compared with baselines (Fig. 1). In the dietary therapy alone group, intakes of total energy and carbohydrates were significantly decreased, whereas the EPA/AA ratio was significantly increased at 6 months compared with baselines, whereas there were no differences in the estimated nutrient intakes in the combined drug treatment group (Table 4). Thus, although all subjects received dietary counseling, the reduction in serum TG levels in the dietary therapy group during the first 6 months of the study period could be attributed to behavioral modification resulting in adequate implementation of the treatment throughout the intervention period, which was not observed in the combined drug treatment group. However, patients in the combined drug treatment group were placed on medication from 7 months onwards, which led to significant reductions in serum TG levels every month thereafter. Previous studies reported that activation of LPL and beta-oxidation of FAs were intensified\(^{20, 21}\), and serum VLDL concentration and TG content in VLDL were decreased\(^{22}\) by activation of PPAR\(\alpha\) with fibrates. Ferramosca et al. reported that \textit{de novo} synthesis of TG in the liver was enhanced with a high carbohydrate diet\(^{23, 24}\); however, there was no significant change in the intake of carbohydrates in the combined drug treatment group during the study period (Table 2). Therefore, it was suggested that the decrease in serum TG levels observed in combined drug treatment group was not the additive effect with diet therapy but the effect of medication alone.

This was consistent with previous results that showed that fibrates and statins, which are included in the medications for dyslipidemia, could reduce serum TG levels by 30%–50% and 10%–30%, respectively\(^{25}\). In a previous study, Yamanaka et al. reported that dietary counseling for patients with diabetes, lead to effects comparable with medical therapy\(^{26, 27}\). The data presented here showed that dietary therapy alone can lower TG levels by 30%–50% and 10%–30%, respectively\(^{25}\). Therefore, it was suggested that the decrease in serum TG levels observed in combined drug treatment group was not the additive effect with diet therapy but the effect of medication alone.
only 30% of patients achieved the target serum TG level of below 1.7 mmol/L by fenofibrate therapy combined with a single lifestyle intervention. However, 76% of subjects in this study achieved the target level at 12 months, an achievement rate that was remarkable. Thus, it is important to continue providing dietary counseling to all patients regardless of therapeutic regimen. With the revision of the medical treatment fee in 2016, the important of nutrition management in medical care was demonstrated, and the number of insurance points for nutritional instruction fee of outpatient was also increased. These results suggest that dietary therapy can replace medications in some cases of hypertriglyceridemia with the objective of reducing medical expenses.

We observed that the number of patients with serum TG levels of 151 – 200 mg/dL at baseline was 81% at the target serum TG level (<150 mg/dL) at 6 months, on the other hand, those with serum TG levels greater than 200 mg/dL, only 50% of patients have cleared the target serum TG level. The improvement in hypertriglyceridemia by dietary therapy alone was observed in mild cases of hypertriglyceridemia, and the decrease in serum TG level was maintained for a long period of time. It should be noted that dietary therapy is the first choice of treatment for patients with mild hypertriglyceridemia. In addition, it is suggested that dietary modifications in combination with medical therapy are more effective for patients with severe hypertriglyceridemia.

Body weight was significantly decreased at 6 and 12 months in both groups compared with baseline (Table 3), and the reductions in body weight were maintained for a long period of time. Obesity is considered an independent risk factor for cardiovascular disease, and it has been reported that it can promote arteriosclerosis indirectly through dyslipidemia, impaired glucose tolerance, and hypertension and directly through adipocytokines such as TNF-α and free FA. Medication alone does not appear to affect body weight, as it has been reported that only 0.55% and 0.36% of patients in the statin monotherapy group and the statin plus fibrate combination therapy group had body weight loss, in a follow-up study that evaluated the effectiveness of monotherapy and combination therapies for cardiovascular outcomes in patients with type 2 diabetes. Although there are few medical intervention studies that emphasized body weight, it is safe to assume that the reduction in body weight observed in both groups of our study were caused by dietary modifications via therapeutic counseling, which is the biggest strength of the dietary therapy in comparison with the medical therapy.

With regard to serum lipid composition, serum SFA weight ratios at 6 and 12 months were significantly decreased compared with baselines in both groups. Furthermore, serum DHA and n-3 PUFA weight ratios in the dietary therapy alone group and serum n-6 PUFA weight ratio in the combined drug treatment group were significantly increased at 6 and 12 months compared with baselines (Table 5). In addition, there were significant increase in the intake of EPA relative to AA and decrease in the intake of n-6 PUFA relative to n-3 PUFA of dietary fat in the dietary therapy alone group, whereas the intake of n-6 PUFA was compared with n-3 PUFA ratio had a tendency to increase in the combined drug treatment group during the intervention period compared with baselines (Table 4). These results suggest that patients in the diet therapy alone group may have been more aware of the increase in dietary fat containing n-3 PUFA. Nevertheless, there were no significant changes in the serum EPA/AA ratio in both groups (Table 5), and it was considered that more intake of EPA was needed to change serum EPA/AA ratio. It has been reported that eicosanoids derived from n-6 PUFA AA are pro-inflammatory and vasoconstriction inducible, whereas those derived from EPA have cardioprotective effects by opposing the effects induced by AA. Consequently, the quality of the PUFA is important. Thus, it is necessary to focus on the quality of the FA during dietary counseling.

Conclusions

In this study, there was about 40% decrease in serum TG level in the dietary therapy alone group after 12 months of evidence-based dietary counseling in line with the guidelines. It is important that the effects of intervention by dietary counseling are publicized to spread its importance and benefits, including lack of side effects and reduction in medical expenses, for hypertriglyceridemia to heighten its awareness to other medical workers and patients in order to encourage its use. This study provides strong evidence that highlight the importance of dietary therapy for hypertriglyceridemia.

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The authors have no conflicts of interest to declare.
References

1) Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, Goldberg AC, Howard WJ, Jacobson MS, Kris-Etherton PM, Lennie TA, Levi M, Mazzone T, Pennathur S. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation, 2011; 123: 2292-2333

2) Iso H, Naito Y, Sato S, Kitamura A, Okamura T, Sankai T, Shimamoto T, Iida M, Komachi Y. Serum triglycerides and risk of coronary heart disease among Japanese men and women. Am J Epidemiol, 2001; 153: 490-499

3) Satoh H, Nishino T, Tomita K, Tsutsui H. Fasting triglyceride is a significant risk factor for coronary artery disease in middle-aged Japanese men. Circ J, 2006; 70: 227-231

4) Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E; PROVE IT-TIMI 22 Investigators. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. J Am Coll Cardiol, 2008; 51: 724-730

5) Noda H, Iso H, Saito I, Konishi M, Inoue M, Tsugane S; JPHC Study Group. The impact of the metabolic syndrome and its components on the incidence of ischemic heart disease and stroke: the Japan public health center-based study. Hypertens Res, 2009; 32: 289-298

6) Teramoto T, et al. Prevention of Atherosclerotic Cardiovascular Diseases 2012, Japan Atherosclerosis

7) Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. Am J Clin Nutr, 2003; 77: 1146-1155

8) Nakanishi N, Tatara K, Nakamura K, Suzuki K. Association of lifestyle with serum lipid levels: a study of middle-aged Japanese men. J Epidemiol, 2000; 10: 117-1162

9) Lopez-Huertas E. The effect of EPA and DHA on metabolic syndrome patients: a systematic review of randomised controlled trials. Br J Nutr, 2012; 107: S185-194

10) Hanwell HE, Kay CD, Lampe JW, Holub BJ, Duncan AM. Acute fish oil and soy isoflavone supplementation increase postprandial serum (n-3) polyunsaturated fatty acids and isoflavones but do not affect triacylglycerols or increase postprandial serum (n-3) polyunsaturated fatty acids and isoflavones in hypertriglyceridemic men. J Nutr, 2009; 139: 1128-1134

11) Kelley DS, Siegel D, Vemuri M, Chung GH, Mackey BE. Docosahexaenoic acid supplementation decreases remnant-like particle-cholesterol and increases the (n-3) index in hypertriglyceridemic men. J Nutr, 2008; 138: 30-35

12) Newens KJ, Thompson AK, Jackson KG, Wright J, Williams CM. DHA-rich fish oil reverses the detrimental effects of saturated fatty acids on postprandial vascular reactivity. Am J Clin Nutr, 2011, 94: 742-748

13) Masuda D, Yamashita S. Postprandial Hyperlipidemia and Remnant Lipoproteins. J Atheroscler Thromb. 2017; 24: 95-109

14) Ding D, Li X, Qiu J, Li R, Zhang Y, Su D, Li Z, Wang M, Lv X, Wang D, Yang Y, Xia M, Li D, Hu G, Ling W. Serum lipids, apolipoproteins, and mortality among coronary artery disease patients. Biomed Res Int, 2014; 709756

15) Yang LG, Song ZX, Yin H, Wang YY, Shi GF, Lu MX, Wang SK, Sun GJ. Low n-6/n-3 PUFA Ratio Improves Lipid Metabolism, Inflammation, Oxidative Stress and Endothelial Function in Rats Using Plant Oils as n-3 Fatty Acid Source. Lipids, 2016; 51: 49-59

16) Tani S, Takahashi A, Nagao K, Hirayama A. Association of Fish Consumption-Derived Ratio of Serum n-3 to n-6 Polyunsaturated Fatty Acids and Cardiovascular Risk With the Prevalence of Coronary Artery Disease. Int Heart J, 2015; 56: 260-268

17) Kobayashi S, Honda S, Murakami K, Sasaki S, Okubo H, Hirota N, Notsu A, Fukui M, Date C. Both comprehensive and brief self-administered diet history questionnaires satisfactorily rank nutrient intakes in Japanese adults. J Epidemiol, 2012; 22: 151-159

18) Kobayashi S, Murakami K, Sasaki S, Okubo H, Hirota N, Notsu A, Fukui M, Date C. Comparison of relative validity of food group intakes estimated by comprehensive and brief-type self-administered diet history questionnaires against 16 d dietary records in Japanese adults. Public Health Nutr, 2011; 14: 1200-1211

19) Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. JAMA, 2002; 288: 2569-2578

20) Auwerx J, Schoonjans K, Fruchart JC, Staels B. Regulation of triglyceride metabolism by PPARs: fibrates and thiazolidinediones have distinct effects. J Atheroscler Thromb, 1996; 3: 81-89

21) Staels B, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart JC. Mechanism of action of fibrates on lipid and lipoprotein metabolism. Circulation, 1998; 98: 2088-2093

22) Vázquez M, Merlos M, Adzet T, Laguna JC. Decreased susceptibility to copper-induced oxidation of rat-lipoproteins after fibrate treatment: influence of fatty acid composition. Br J Clin Pharmacol, 1996; 117: 1155-1162

23) Ferramosca A, Conte A, Damiano F, Siculella L, Zarà L. Differential effects of high-carbohydrate and high-fat diets on hepatic lipogenesis in rats. Eur J Nutr, 2014; 53: 1103-1114

24) Chong MF, Hodson L, Bickerton AS, Roberts R, Neville M, Karpe F, Frayn KN, Fielding BA. Parallel activation of de novo lipogenesis and stearoyl-CoA desaturase activity after 3 d of high-carbohydrate feeding. Am J Clin Nutr, 2008; 87: 817-823

25) Talayero BG, Sacks FM. The role of triglycerides in atherosclerosis. Curr Cardiol Rep, 2011; 13: 544-552

26) Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med, 2002; 346: 393-403

27) Lindström J, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, Hjemdahl P, Härkönen P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Mannelin M, Paturi M, Sundvall J, Valle TT, Uusitupa M, Tuomilehto J; Finnish Diabetes Prevention Study Group. The impact of the metabolic syndrome and its components on the incidence of ischemic heart disease and stroke: the Finnish Diabetes Prevention Study. Lancet, 2006; 368: 1673-1679

28) Rosolová H, Bláha V, Ceska R, Hamouz Z, Pelikánová T, Sucharda P. The effect of treatment with fenofibrate on the risk profile of patients with metabolic syndrome and mixed dyslipidemia treated on an
outpatient basis. Vnitr Lek, 2007; 53: 339-346
29) Lapidus L, Bengtsson C, Larsson B, Pennert K, Rybo E, Sjöström L. Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden. Br Med J (Clin Res Ed), 1984; 289: 1257-1261
30) Larsson B, Svärdsudd K, Welin L, Wilhelmsen L, Björntorp P, Tibblin G. Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. Br Med J (Clin Res Ed), 1984; 288: 1401-1404
31) Carr DB, Utzschneider KM, Hull RL, Kodama K, Rettzlaff BM, Brunzell JD, Shofer JB, Fish BE, Knopp RH, Kahn SE. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. Diabates, 2004; 53: 2087-2094
32) Matsuzawa Y. The metabolic syndrome and adipokines. FEBS Lett, 2004; 22: 2917-2921
33) Suh HS, Hay JW, Johnson KA, Doctor JN. Comparative effectiveness of statin plus fibrate combination therapy and statin monotherapy in patients with type 2 diabetes: use of propensity-score and instrumental variable methods to adjust for treatment-selection bias. Pharmacoeconomics, 2012; 21: 470-484
34) Blok WL, Katan MB, van der Meer JW. Modulation of inflammation and cytokine production by dietary (n-3) fatty acids. J Nutr, 1996; 126: 1515-1533
35) Maruyama C, Nakano R, Shima M, Mae A, Shijo Y, Nakamura E, Okabe Y, Park S, Kameyama N, Hirai S, Nakanishi M, Uchida K, Nishiyama H. Effects of a Japan Diet Intake Program on Metabolic Parameters in Middle-Aged Men. J Atheroscler Thromb. 2017; 24: 393-401