Original Paper

Chronic Effect of Dietitian-Led Nutrition Therapy of Food Order on Diabetic Complications and Intima Media Thickness in Outpatients with Type 2 Diabetes at Primary Care Clinic after 4 years: Retrospective Cohort Study

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Abstract

The aim of this retrospective cohort study was to evaluate the effect of 4-year-dietitian-led medical nutrition therapy on diabetic complications and carotid intima media thickness (IMT) in outpatients with type 2 diabetes (T2DM) at a primary care clinic. Eighty-three participants were provided with dietitian-led medical nutrition therapy focusing food order "eating vegetable before carbohydrate" based on the Japan Diet (intervention group) and 78 participants were provided without dietitian-led nutrition therapy (control group). The two groups were compared for progression of diabetic complications and IMT for 4 years. After 4 years significant improvements in HbA1c (8.2 ± 1.4% to 7.6 ± 1.0%, $p < 0.01$), systolic blood pressure, and diastolic blood pressure were observed in the intervention group, whereas Total Cholesterol and LDL-Cholesterol were improved in the control group. The dietitian-led nutrition therapy with food order was effective to prevent diabetic complications including cerebrovascular disease, hypertension, and dyslipidemia while the ratio of atherosclerosis and cerebrovascular disease increased in the control group after 4 years. Maximum IMT decreased slightly in both groups (intervention group; 1.051 to 1.022 mm, control group; 1.019 to 0.994 mm), although the decrement was neither statistically significant between groups nor before and after the medical treatments. This result indicates that the dietitian-led nutrition therapy with food order was effective on glycemic control and suppression of diabetic complications, such as atherosclerosis, cerebrovascular disease, and hypertension, but both medical nutrition therapy and regular medical treatments are effective in suppressing the progression of IMT for 4 years in individuals with T2DM.

Keywords: type 2 diabetes, medical nutrition therapy, dietitian, intima media thickness, food order

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Introduction

Macrovascular disease is a major cause of death in individuals with diabetes. The risks of ischemic heart disease and cerebrovascular disease in individuals with diabetes are 2- to 4-fold higher than those risk in individuals without diabetes[1–4]. Hyperglycemia and large amplitude of glycemic excursions are associated with increased risk of atherosclerosis in people with and without type 2 diabetes (T2DM)[5] as well as hypoglycemia are associated with increased risk of vascular events and dementia[6,7]. Therefore, minimizing the mean amplitude of glycemic excursion (MAGE) by pharmacological and medical nutrition therapy is important for preventing cerebrovascular disease or cardiovascular disease in individuals with diabetes. The chronic effects of lifestyle, particularly diet, on atherosclerosis progression and cardiovascular risk have been reported[8–15], however, the effects of long-term dietary intervention on progression of atherosclerosis in individuals with T2DM are still controversy[16, 17].

We have reported previously that the significant effects of food order 'eating vegetables before carbohydrates' based on the Japan Diet instructed by dietitians on the long-term glycemic control and diastolic blood pressure (DBP), and that the regimen was

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effective for preventing increase of the diabetic complications, such as atherosclerosis for 5 years in outpatients with T2DM at primary care clinics[18–20]. In the Japan Diet, the higher consumption of fish, soybeans and soy products, vegetable, mushrooms, seaweeds, and unrefined cereal, as well as lower consumption of animal fat, meat, and sweet were recommend to prevent atherosclerosis.

The aim of this study was to determine the effect of dietitian-led medical nutrition therapy for T2DM on carotid intima media thickness (IMT) and prevention of diabetic complications. In this retrospective cohort study, we assessed the effect on diabetic complications and IMT of the 4-year follow-up of dietitian-led medical nutrition therapy that was focusing on food order based on the Japan Diet in outpatients with T2DM at primary care clinic.

Materials and Methods

Participants

We recruited diagnosed outpatients who fulfilled the World Health Organization (WHO) criteria for T2DM at Kajiyama Clinic, which is the primary care clinic for diabetes in Kyoto, Japan. For the patients who agreed to participate the study, IMT was measured at baseline and after medical treatments. The period of intervention was from 2004 to 2009, and the 4-year follow-up was performed from 2008 to 2014. The exclusion criteria for participants were as follows: the participants (1) who took only baseline IMT examination (2) with chronic kidney disease stage 4 (3) with alcoholic or mental illness. The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Kyoto Women's University (27-10). Informed consent was obtained from all participants prior to the study.

The Medical Nutrition Therapy of Food Order in the Intervention Group

The participate who agreed with the terms of the study and whose IMT at baseline and after the medical treatment were provided at the clinic, were divided into two groups; the participants with the dietitian-led medical nutrition therapy (the intervention group) and the participants without the dietitian-led medical nutrition therapy (the control group) (Figure 1). The participants in the intervention group received individual medical nutrition therapy by registered dietitians once in every 1 to 2 months. The dietitian-led medical nutrition therapy has focused on the food order based on the Japan Diet. In addition to the instruction of food order the medical nutrition therapy includes planning menu and making appropriate food choices for each participant.

Our original dietary method of food order "eating vegetable before carbohydrate" has been reported and was confirmed to be effective on acute[18, 19] and chronic glycemic control[20]. This simple and easy dietary method of food order is consisted of 3 steps, eating vegetables first for 5 min, the main dish for 5 min, and carbohydrate at the end for 5 min[19]. The participants were recommended to eat more than 350 g per day of vegetables, mushrooms, and seaweeds and to decrease the intake of sweetened beverage, sweets, meat, eggs, and fruits. The dietitians of the study group gave face-to-face counseling on individual practical glycemic goals according to the patient's current dietary intake, lifestyle, and socioeconomically situations. To assess the dietary intake, the dietitians interviewed each participant in the intervention group to receive more accurate dietary intake based on the 3 days dietary report by the participants at initial visit and after 6 months. Dietary intake was assessed, and its nutritional intake was calculated using a computer software (Eiyokun, Kenpakusya, Tokyo, Japan) by the dietitians. The time required for medical nutrition therapy was approximately 30 min at the initial visit and 20 min for the subsequent sessions. On the other hand, the participants in the control group were not provided with the medical nutrition therapy by the dietitians, but only received routine doctor's consultation once in every 1 to 2 months and the brief dietary advice was given by physicians and nurses.

Laboratory Analyses

In the baseline examination, data including age, sex, duration of DM, medication use were obtained from each participant by medical staffs at the clinic. Anthropometric and blood pressure measures were obtained from all participants by nurses of the clinic at baseline and subsequently once in every 1 to 2 months.

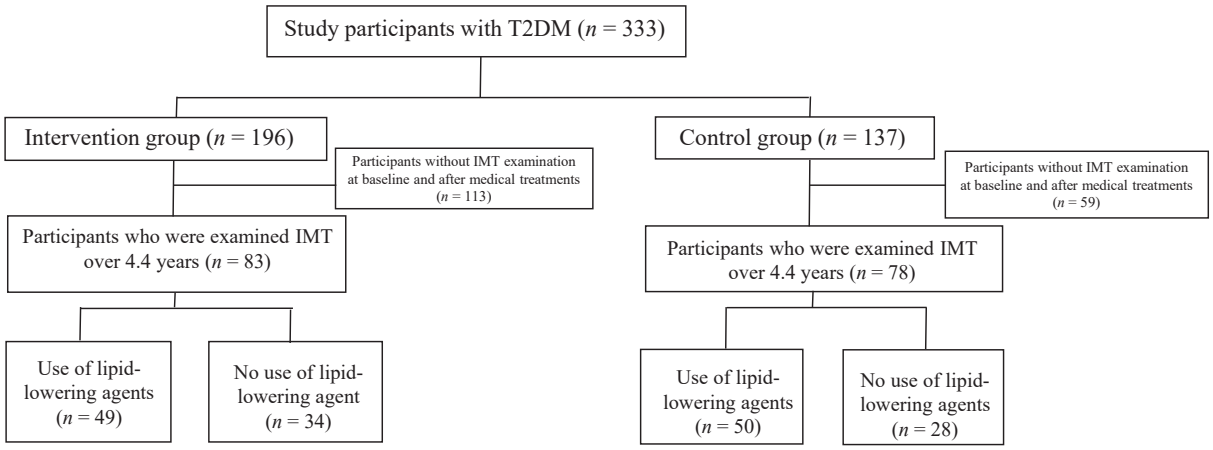

Figure 1. Study flow

Blood pressure was measured twice in the seated position during the physical examination after the participants had rested for 10 min at the clinic. Blood samples were collected from all participants once in every 1 to 2 months at the clinic. HbA1c levels were determined by high-performance liquid chromatography (HPLC) method (ADAMS^{TM} HA-8160, Arkray Inc, Kyoto, Japan). Total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels were determined by enzymatic method (Chemical Autoanalyzer, Hitachi Co. Tokyo, Japan). Carotid IMT in right and left carotid arteries were measured by ultrasonography echo (ALOKA Prosound56, Hitachi Aloka Medical, Tokyo, Japan) by technicians without knowing whether the participants belonged to the intervention or the control group. Both right and left carotid arteries were examined at levels of the distal common carotid artery, 1.0 cm proximal to the carotid bulb, and the proximal internal carotid artery in both transverse and longitudinal orientations by technicians as a prescribed protocol[21]. IMT measures were performed at all three segments providing a total of 6 measurements per patient. The IMT was defined as the distance between the adventitia-media interface and intima-lumen interface. The maximum value of the 6 measurements from the bilateral IMTs was used in the analysis. One end-diastolic frame for each interrogation angle was selected and analyzed for mean and max IMT. The primary outcome was HbA1c and the secondary outcomes were mean IMT and max IMT.

Statistical Analysis

The results are expressed as mean ± SEM unless otherwise stated. General characteristics and the outcomes were compared between groups using chi-square or Mann–Whitney U test. Since we could not statistically confirm homogeneity of variance and normal distribution for some parameters by Shapiro-Wink and Levene's tests, we used a paired comparison by Wilcoxon matched-pairs signed-rank test for comparison between before and after the medical treatment within a same participant. Differences were considered significant at $p < 0.05$. All analyses were performed with SPSS Statistics ver. 24 software (IBM Corp., Armonk, NY, USA).

Results

Excluding the participants whose IMT data was not obtained after the medical treatment at the clinic, the data were obtained from 83 participants in the intervention group and 78 participants in the control group (Figure 1). At the baseline level, there was no significant difference in the characteristic and pharmacotherapy between the intervention and the control group (Table 1 and 5). The mean number of the dietary sessions were 12.0 times (5.8-22.0 times; 25% - 75% percentile value) in the intervention group.

The changes in HbA1c, blood pressure, serum lipid concentrations, and mean and max IMT were shown in Table 2. After dietitian-led medical nutrition therapy, HbA1c, SBP, and DBP were significantly reduced in the intervention group, whereas in the control group, TC and LDL-C were significantly reduced after the medical treatment. On the other hand, max IMT decreased slightly in both group after intervention, while mean IMT increased slightly in both groups, although none of the IMT changes were statistically significant. Also, there was no significant difference between men and women of mean and max IMT (data not shown). Comparing serum lipid profiles and IMT in both groups with and without use of lipid-lowering agents, the significant reduction of TC and LDL-C were observed in the participants who used lipid-lowering agents in both groups. The reduction of TG was observed in the participants who used lipid-lowering agents in the intervention group, whereas TC decreased

Table 1. Characteristics of participants with type 2 diabetes who continued to receive the medical treatment at the clinic for 4 years at baseline in both groups

	Intervention group (n = 83)	Control group (n = 78)	p
Male/Female (n)	36 / 47	42/ 36	0.184
Age (years)	67.2 ± 8.6	68.7 ± 10.2	0.300
Duration of diabetes (years)	8.1 ± 9.2	8.1 ± 6.5	0.313
Body Weight (kg)	61.7 ± 13.8	62.7 ± 12.8	0.476
BMI (kg/m^2)	24.6 ± 4.7	23.6 ± 3.1	0.672
HbA1c (%) (mmol/mol)	8.2 ± 1.4 (66)	7.8 ± 1.3 (61)	0.084
SBP (mmHg)	130 ± 15	132 ± 16	0.524
DBP (mmHg)	74 ± 11	71 ± 9	0.187
Total-C (mg/dL)	211 ± 38	206 ± 33	0.388
LDL-C (mg/dL)	131 ± 33	123 ± 27	0.171
HDL-C (mg/dL)	53 ± 11	57 ± 15	0.136
TG (mg/dL)	139 ± 84	140 ± 78	0.665
Max IMT (mm)	1.051 ± 0.433	1.019 ± 0.316	0.642
Mean IMT (mm)	0.816 ± 0.244	0.792 ± 0.132	0.642

Data are mean ± SD or n. General characteristics and the outcomes were compared between groups using chi-square and Mann-Whitney U test. BMI; body mass index, SBP; systolic blood pressure, DBP; diastolic blood pressure, Total-C; total cholesterol, LDL-C; low density lipoprotein cholesterol, HDL-C; high density lipoprotein cholesterol, TG; triglyceride, OHA; oral hypoglycemic agents, α-GI inhibitor; alpha-glucosidase inhibitor. Max IMT; maximum IMT.

Table 2. Changes in glycemic control, blood pressure, lipid profile, and IMT at baseline and after medical treatment in participants with type 2 diabetes of both groups

	Intervention group (n = 83)		Control group (n = 78)	
	Baseline	After 4 years	Baseline	After 4 years
BMI (kg/m^2)	24.6 ± 4.7	24.2 ± 5.1	23.6 ± 3.1	23.6 ± 4.0
HbA1c (%) (mmol/mol)	8.2 ± 1.4 (66)	7.6 ± 1.0 (59) ***	7.8 ± 1.3 (61)	7.8 ± 1.2 (61)
SBP (mmHg)	130 ± 15	126 ± 11 *†	132 ± 16	127 ± 19
DBP (mmHg)	74 ± 11	69 ± 8 ***	71 ± 9	69 ± 7
Total-C (mg/dl)	211 ± 38	194 ± 30	206 ± 33	187 ± 31 ***
LDL-C (mg/dl)	131± 33	117 ±30	123 ± 27	106 ± 26 ***†
HDL-C (mg/dl)	53 ± 11	56 ± 14	57 ± 15	59 ± 16
TG (mg/dl)	139 ± 84	125 ± 66	140 ± 78	134 ± 77
Max IMT (mm)	1.051 ± 0.433	1.022 ± 0.280	1.019 ± 0.316	0.994 ± 0.251
Mean IMT (mm)	0.816 ± 0.244	0.827± 0.201	0.792 ± 0.132	0.812 ± 0.175

Data are mean ± SD. The parameters were compared between groups by Mann-Whitney U test. Wilcoxon matched-pairs signed-rank test were used for comparison between before and after medical treatment. BMI; body mass index, SBP; systolic blood pressure, DBP; diastolic blood pressure, Total-C; total cholesterol, LDL-C; low density lipoprotein cholesterol, HDL-C; high density lipoprotein cholesterol, TG; triglyceride. Max IMT; maximum IMT. Baseline vs. after intervention; $^{*}p < 0.05$, $^{***}p < 0.001$. Intervention group vs. Control group; $^{\dagger}p < 0.05$.

Table 3. Changes of serum lipid profiles and mean and max IMT in participants with and without use of lipid-lowering agents

	Intervention group (n = 83)		Control group (n = 78)	
	Lipid-lowering agent (n = 49)	No use of lipid-lowering agent (n = 34)	Lipid-lowering agent (n = 50)	No use of Lipid-lowering agent (n = 28)
Baseline Total-C (mg/dl)	216 ± 39	204 ± 36	209 ± 33	199 ± 33
After 4 years Total-C (mg/dl)	− 24 ± 31 *	− 6 ± 29	− 19 ± 32 **	− 18 ± 28 *†
Baselinte LDL-C (mg/dl)	132 ± 36	129 ± 28	123 ± 28	124 ± 26
After 4 years LDL-C (mg/dl)	− 19 ± 31 *	− 6 ± 29	− 18 ± 28 **	− 16 ± 23
Baseline HDL-C (mg/dl)	54 ± 11	52 ± 12	59 ± 16	54 ± 12
After 4 years HDL-C (mg/dl)	3 ± 15	2 ± 13	2 ± 16	1 ± 13
Baseline TG (mg/dl)	151 ± 91	120 ± 68 ‡	152 ± 87	119 ± 52
After 4 years TG (mg/dl)	− 34 ± 57 *	17 ± 77	− 15 ± 76	11 ± 79
Max IMT (mm)	1.130 ± 0.517	0.937 ± 0.234 ‡	1.034 ± 0.363	0.992 ± 0.221
After 4 years Max IMT (mm)	− 0.069 ± 0.288	0.029 ± 0.262	− 0.026 ± 0.275	− 0.023 ± 0.203
Mean IMT (mm)	0.869 ± 0.277	0.740 ± 0.165 †‡‡	0.793 ± 0.134	0.791 ± 0.132
After 4 years Mean IMT (mm)	− 0.005 ± 0.225	0.034 ± 0.147	0.076 ± 0.178	0.025 ± 0.174

Data are mean ± SD. The parameters were compared between groups by Mann–Whitney U test. Wilcoxon matched-pairs signed-rank test were used for comparison between before and after medical treatment. Total-C; total cholesterol, LDL-C; low density lipoprotein cholesterol, HDL-C; high density lipoprotein cholesterol, TG; triglyceride, Max IMT; maximum IMT. Baseline vs. after intervention; $^{*}p < 0.05$, $^{**}p < 0.01$. Intervention group vs. Control group; $^{\dagger}p < 0.05$. Lipid-lowering agent vs. No use of Lipid-lowering agent; $^{\ddagger}p < 0.05$, $^{\ddagger\ddagger}p < 0.01$.

Table 4. Micro- and macro-vascular complications, hypertension, dyslipidemia at baseline and after 4 years in participants with type 2 diabetes of both groups

	Intervention group (n = 83)		Control group (n = 78)	
	Baseline	After 4 years	Baseline	After 4 years
Diabetic nephropathy, n (%)	1 (1)	3 (4)	3 (4)	3 (4)
Diabetic neuropathy, n (%)	5 (6)	12 (14)	4 (5)	6 (8)
Atherosclerosis, n (%)	48 (58)	54 (65)	39 (50)	64 (82) ***†
Coronary heart disease, n (%)	11 (13)	11 (13)	7 (9)	12 (15)
Cerebrovascular disease, n (%)	16 (19)	20 (24)	12 (15)	23 (29) *
Hypertension, n (%)	29 (35)	31 (37)	22 (28)	31 (40)
Dyslipidemia, n (%)	39 (47)	40 (48)	52 (67) †	60 (77) †††

Number of the participants with diabetic complications were compared between groups using chi-square test. Baseline vs. after intervention; $^{*}p < 0.05$, $^{***}p < 0.001$. Intervention group vs. control group; $^{\dagger}p < 0.05$, $^{\dagger\dagger\dagger}p < 0.001$.

Table 5. The number of participants with type 2 diabetes with pharmacologic agents at baseline and after 4 years in both groups

	Intervention group (n = 83)		Control group (n = 78)	
	Baseline	After 4 years	Baseline	After 4 years
No use of insulin or OHA, *n* (%)	32 (39)	27 (33)	23 (29)	22 (28)
No use of antihypertensive agent, *n* (%)	61 (73)	52 (63)	60 (77)	57 (73)
No use of lipid-lowering agent, *n* (%)	52 (63)	33 (40) **	39 (50)	27 (35)
Insulin, *n* (%)	5 (6)	5 (6)	8 (10)	9 (12)
OHA, *n* (%)	48 (58)	53 (64)	51 (65)	52 (67)
Sulfonylurea, *n* (%)	36 (43)	42 (51)	39 (50)	42 (54)
Metformin, *n* (%)	13 (16)	20 (24)	13 (17)	30 (38) **†
α-GI inhibitor, *n* (%)	22 (27)	25 (30)	30 (38)	29 (37)
Glinide, *n* (%)	3 (4)	2 (2)	0 (0)	1 (1)
Thiazolidinedione, *n* (%)	7 (8)	7 (8)	4 (5)	7 (9)
Antihypertensive agent, *n* (%)	22 (27)	31 (37)	18 (23)	21 (27)
Lipid-lowering agent, *n* (%)	31 (37)	50 (60) **	39 (50)	51 (65)
HMG-CoA reductase inhibitor, *n* (%)	28 (34)	41 (49) *	37 (47)	49 (63)
Anion-exchange resin, *n* (%)	1 (1)	1(1)	2 (3)	1 (1)
Nicotinic acid, *n* (%)	0 (0)	0 (0)	1 (1)	1 (1)
Fibrate, *n* (%)	2 (2)	3 (4)	1 (1)	1 (1)
EPA, *n* (%)	1 (1)	4 (5)	2 (3)	1 (1)
Ezetimibe, *n* (%)	0 (0)	5 (6) *	0 (0)	1 (1)

Number of the participants with and without pharmacologic agents were compared between groups using chi-square test. OHA; oral hypoglycemic agent. α-GI inhibitor; alpha-glucosidase inhibitor. HMG-CoA reductase inhibitor; hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitor, EPA; eicosapentaenoic acid. Baseline vs. after 4 years; $^{*}p < 0.05$, $^{**}p < 0.01$, Intervention group vs. control group; $^{\dagger}p < 0.05$.

in the participants without use of lipid-lowering agents in the control group (Table 3). The reduction of max IMT were observed in the participants using lipid-lowering agents in both groups, and in the participants not using lipid-lowering agent in the control group, however, none of these changes were statistically significant.

In terms of diabetic complications, the ratio of atherosclerosis[22], cerebrovascular disease[23] increased in the control group after 4 years. However, in the intervention group no significant increase was demonstrated in both micro and macrovascular complication, hypertension, and dyslipidemia. The ratio of atherosclerosis and dyslipidemia in the control group was higher than those of in the intervention group after 4 years (Table 4). The data from participants with pharmacological agents at baseline and after intervention were shown in Table 5. The ratio of participants using lipid-lowering agents, particularly hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitor increased in the intervention group, while the number of participants with metformin were increased and the ratio of participants using it was higher in the control group.

Even after excluding the effect of oral hypoglycemic agents and insulin, the improvement of HbA1c were observed to be evident in the intervention group after the dietary education, although no improvement was observed in the control group (Supplement materials, Table S1A). Max IMT decreased after 4 years in both groups, -0.028 in the intervention group and -0.011 in the control group, but no significant difference was observed in participants without use and without changes of insulin or OHA in between groups or before and after the medical treatment. The participants without use and without change of antihypertensive agents in the intervention group showed significant reduction of DBP, but no change was observed in the control group (Table S1B). Max IMT decreased in both groups, but none of the changes were significant after 4 years in participants without use and without changes of antihypertensive in both groups. The participants without use and without change of lipid-lowering agents decreased BMI significantly in the intervention group while TC and LDL-C decreased in the control group. Insignificant reduction of Max IMT was observed in both groups (Table S1C).

The nutrient intake in the intervention group has been reported in our previous paper[20]. As we mentioned in the previous report the intake of energy, protein, fat, carbohydrate, and salt all decreased whereas the intake of dietary fiber increased in the intervention group after the medical nutrition therapy. The participants in the intervention group increased the consumption of vegetables, while the consumption of grains, meats, eggs, fruits, sweetened beverages, sugar, sweets, snacks, and oil were decreased.

Discussion

To the best of our knowledge, the current study is the first study to evaluate the chronic effect of dietitian-led medical nutrition therapy on changes of IMT as well as progression of diabetic complications at primary care clinics in outpatients with T2DM. We observed significant improvements in HbA1c and DBP in the intervention group even in participants without use and without changes of insulin, OHA, or antihypertensive agents in the intervention group. The ratio of micro and macro diabetic complications, hypertension, and dyslipidemia in the intervention

Table S1A. Changes in glycemic control and IMT in participants with type 2 diabetes without use and without change of insulin or OHA in both groups

	Intervention group (n = 62)			Control group (n = 54)		
	Baseline	After 4 years		Baseline	After 4 years	
Male/Female (n)	26 /36	–		27 / 27	–	
Age (years)	67.5 ± 9.0			68.3 ± 11.0		
Duration of Diabetes (years)	8.5 ± 9.9			7.4 ± 7.9		
BMI (kg/m^2)	24.1 ± 4.1	23.6 ± 4.3		22.6 ± 2.6	22.8 ± 3.0	
HbA1c (%) (mmol/mol)	8.1 ± 1.4 (65)	7.4 ± 0.9 (57) **		7.5 ± 1.2 (58) †	7.6 ± 1.2 (59)	
Max IMT (mm)	1.007 ± 0.367	0.979 ± 0.245	− 0.028	0.961 ± 0.170	0.950 ± 0.201	− 0.011
Mean IMT (mm)	0.795 ± 0.244	0.802 ± 0.187	+ 0.007	0.780 ± 0.132	0.786 ± 0.160	+ 0.006

Data are mean ± SD or n. The parameters were compared between groups using Mann–Whitney U test. Wilcoxon matched-pairs signed-rank test were used for comparison between before and after medical treatment. OHA; oral hypoglycemic agents, BMI; body mass index. Max IMT; maximum IMT. Baseline vs. after intervention; $^{**}p$ <0.01, Intervention group vs. control group; $^{\dagger}p < 0.05$.

Table S1B. Changes in blood pressure and IMT in participants with type 2 diabetes without use and without change of antihypertensive in both groups

	Intervention group (n = 67)			Control group (n = 73)		
	Baseline	After 4 years		Baseline	After 4 years	
Male/Female (n)	27 / 40	–		40 / 33	–	
Age (years)	66.4 ± 8.7			68.1 ± 10.3		
Duration of Diabetes (years)	7.8 ± 9.6			8.2 ± 6.6		
BMI (kg/m^2)	24.8 ± 4.7	24.3 ± 5.2		23.7 ± 3.1	23.7 ± 4.1	
SBP (mmHg)	129 ± 15	126 ± 13		131 ± 15	127 ± 19	
DBP (mmHg)	73 ± 11	68 ± 8 **		71 ± 10	70 ± 7	
Max IMT (mm)	1.024 ± 0.365	1.004 ± 0.273	− 0.020	1.020 ± 0.327	0.998 ± 0.256	− 0.022
Mean IMT (mm)	0.807 ± 0.249	0.815 ± 0.201	+ 0.008	0.790 ± 0.136	0.813 ± 0.179	+ 0.023

Data are mean ± SD or n. The parameters were compared between groups using Mann–Whitney U test. Wilcoxon matched-pairs signed-rank test were used for comparison between before and after medical treatment. BMI; body mass index, SBP; systolic blood pressure, DBP; diastolic blood pressure. Max IMT; maximum IMT. Baseline vs. after intervention; $^{**}p < 0.01$.

Table S1C. Changes in lipid profile in participants with type 2 diabetes without use and without change of lipid-lowering agents in both groups

	Intervention group (n = 60)			Control group (n = 60)		
	Baseline	After 4 years		Baseline	After 4 years	
Male/Female (n)	25 / 35	–		30 / 30	–	
Age (years)	66.9 ± 8.7			69.6 ± 10.2		
Duration of Diabetes (years)	6.7 ± 7.6			7.6 ± 7.6		
BMI (kg/m^2)	24.7 ± 4.4	24.0 ± 4.9 *		23.2 ± 3.6	22.6 ± 4.0	
Total-C (mg/dl)	207 ± 32	193 ± 28		201 ± 29	187 ± 32 **	
LDL-C (mg/dl)	130 ± 31	118 ± 28		121 ± 23	107 ± 27 *	
HDL-C (mg/dl)	53 ± 10	55 ± 13		57 ± 16	59 ± 17	
TG (mg/dl)	121 ± 54	123 ± 62		141 ± 76	139 ± 77	
Max IMT (mm)	1.007 ± 0.368	0.991 ± 0.258	− 0.015	1.012 ± 0.337	0.978 ± 0.254	− 0.035
Mean IMT (mm)	0.795 ± 0.254	0.801 ± 0.181	+ 0.006	0.790 ± 0.138	0.802 ± 0.182	+ 0.012

Data are mean ± SD or n. The parameters were compared between groups using Mann–Whitney U test. Wilcoxon matched-pairs signed-rank test were used for comparison between before and after medical treatment. BMI; body mass index, Total-C; total cholesterol, LDL-C; low density lipoprotein cholesterol, HDL-C; high density lipoprotein cholesterol, TG; triglyceride. Max IMT; maximum IMT. Baseline vs. after intervention; $^{*}p < 0.05$, $^{**}p$ <0.01.

group showed no change, whereas the ratio of atherosclerosis and cerebrovascular disease increased significantly in the control group after 4 years.

Although the current study demonstrated slight reduction in max IMT in both groups after 4 years, these reduction in max IMT were neither significantly different between two groups nor between with and without lipid-lowering agents in any groups after the medical treatment. Carotid IMT has become an independent predictor for future cardiovascular events, stroke, or myocardial infarction[24–27]. Several reports have indicated that the mean IMT progression in individuals with diabetes ranged between 0.03 to 0.04 mm per year[28, 29]. In the meta-analysis, it was revealed that increment of 0.1 mm in IMT rose the future risk of myocardial infarction by 10-15%, and the stroke risk by 13-18%[30] while a reduction of IMT per 0.1 mm per year reduced the relative risk for cardiovascular disease by 9%[31]. In this study, both the dietitian-led nutrition therapy and medical treatments may suppress the progression of IMT for 4 years in individuals with T2DM.

Many lipid-lowering drugs affect plasma lipid profiles as well as progression of atherosclerosis and cardiovascular disease. In the present study, more than half of the participants were taking lipid-lowering agents after 4 years, 60% for the intervention group and 65% for the control group. Systematic review and meta-analysis have demonstrated that statins can significantly reduce the carotid IMT compared with placebo or usual care[28]. However, Huang Y *et al.* reported that the effect of lipid-lowering agents on reduction of carotid IMT was significant in the presence of carotid atherosclerosis or coronary artery diseases, but not in the setting of primary prevention of carotid atherosclerosis or coronary artery diseases[32]. The reason for insignificant changes observed in IMT in this study might be due that the values of max and mean IMT at the baseline were not as severe in the participants of both groups as reported by Huang Y.

Lifestyle, particularly diet affects cardiovascular risk, but there is no consensus about the best dietary model for the secondary prevention of cardiovascular disease in individuals with T2DM. There are many reports that Mediterranean diet could protect against the development of the atherosclerotic plaque and can decrease overall vascular events[8, 10–12]. Jimenez-Torres *et al.* reported that Mediterranean diet rich in extra-virgin olive oil was associated with decreased atherosclerosis progression, reduced IMT and carotid plaque height compared to a low-fat diet[31]. On the other hand, Mediterranean diet has been reported not to be associated with IMT but could reduce the carotid atherosclerotic plaque and stroke risk[16, 17]. The PREDIMED Study has reported that the incidence of major cardiovascular events was lower among those assigned to Mediterranean diet supplemented with extra-virgin olive oil or nuts than among those assigned to reduced fat diet[11]. Thus, the effect of Mediterranean diet on reduction of risk of cardiovascular disease is still controversial. The Dietary Approach to Stop Hypertension (DASH) has reported that long-term adherence to the DASH diet was associated with decreased IMT values[14]. An appropriate diet quality of the Alternate Health Eating Index was associated with a greater IMT regression following a two-year intervention among individuals with type 1 and type 2 diabetes[15]. Petersen KS.*et.al.* had reported that increasing fruit and vegetable intakes for 12-month showed IMT improvement in individuals with type 1 and type 2 diabetes[34].

Recent review articles concluded that plant-based food was associated with reduced risk of cardiovascular disease, ischemic heart disease, and T2DM[35]. In our study, dietary education focused on the Japan Diet with food order which recommended consuming vegetable, mushroom, seaweeds, fresh fish, soybeans, and soy products, and unprocessed grains, but decreasing the consumption of sugar, sweet, sweetened beverages. However, we did not strictly encourage to change their diet entirely to the plant-based whole food. If the dietary education focused more on plant-based whole food, the different results and conclusions might have been driven.

The present study has some potential limitations that should be considered. First, this is a retrospective cohort study, not randomized controlled trial, conducted at a single primary care clinic in the small population of our participants, and the results were obtained from participants who took IMT measurement at the clinic twice at baseline and after the medical care in both groups. Therefore, the participants in both groups of the present study, particularly in the intervention group, might be considered as highly motivated individuals with good adherence, and this might have biased the results. Additionally, the nutrition intake and changes after the medical treatment in the control group were unknown because the dietitian-led nutritional intervention was not done in the control group. Second, IMT measurement should be combined with other measurements, such as plaque measurements to provide higher prediction for cardiovascular events, because cardiovascular disease occurs when an atherosclerotic plaque ruptures or erodes[36]. Also, pulse wave velocity (PWV) and ankle brachial pressure index (ABI) should have been measured in this study. Third, since this study was conducted in the long-term period, the examinations of IMT were not done by the same technician, leaving possibility that the data obtained may have certain variation due to differences in the measurement of each technician. Fourth, other factors such as hyperuricemia might affect the result because hyperuricemia has been reported as the risk marker for cardiovascular disease and higher ratio of death by cardiovascular disease[37]. Therefore, further investigations of association between dietary intervention and progression of IMT are required in the future.

Conclusion

This result indicates that the dietitian-led nutrition therapy with food order was effective on glycemic control and suppression of diabetic complications, such as atherosclerosis, cerebrovascular disease, and hypertension after 4 years. However, the changes of IMT in both groups were not statistically significant after intervention. This indicates that both dietitian-led nutrition therapy and regular medical treatments are effective in suppressing the progression of IMT for 4 years in individuals with T2DM.

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