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Dietary instructions focusing on meal-sequence and nutritional balance for prediabetes subjects: An exploratory, cluster-randomized, prospective, open-label, clinical trial

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ABSTRACT

Background: Although lifestyle modifications are known to be effective in type 2 diabetes (T2D) as well as in prediabetes, adherence to a healthy diet is difficult for some, and interventions of lifestyle modifications need to be revised occasionally. Meal sequence has been gaining attention as a part of a healthy diet among T2D individuals to improve glycemia and body weight. In addition, a dietary instruction program, SMART Washoku®, which can help individuals to consume a more nutritionally balanced diet, has been developed.

Methods: The current exploratory trial was designed to examine the effects of dietary instructions focusing on meal sequence and nutritional balance in individuals with prediabetes in the Japanese national health check-up and guidance program. Participants were cluster-randomized into three groups: Group A, receiving a conventional health guidance program ($n = 11$); Group B, receiving health guidance with dietary instructions focusing on meal sequence ($n = 18$); and Group C, receiving health guidance with dietary instructions focusing on nutritional balance ($n = 13$). Participants received health guidance education and various measurements before and 6 months after the instructions.

Results: Body weight in Group B was significantly reduced compared to that in Group A, with similar adherence, while the effects on glycemia were similar between the two Groups. Body weight reduction was greater in Group C compared to that in Group A, although adherence in Group C was significantly lower than that in Group A.

Conclusion: The group receiving health guidance with dietary instructions focusing on meal sequence exhibited similar adherence and greater reduction in body weight than the group receiving conventional health guidance.

1. Introduction

The rapid increase in type 2 diabetes (T2D) is one of the most serious global health problems today. The number of patients with diabetes, estimated to be 425 million in 2017, is expected to rise to 629 million by 2045.[1] The etiology of T2D involves lifestyle factors such as dietary habits and physical activity as well as aging and genetic predispositions, all of which influence insulin secretion from the pancreatic β-cells and/

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or reduce insulin sensitivity of target organs. Previous studies demonstrated that lifestyle modifications are effective in T2D prevention and obesity.[2–5] However, adherence to a healthy diet and an exercise program is difficult for some individuals,[6,7] and interventions of lifestyle modifications need to be improved from time to time.

Meal sequence has been gaining much attention as part of a healthy diet among individuals with T2D. It has been demonstrated that consumption of vegetable dishes before carbohydrate dishes acutely improves postprandial glucose excursion in individuals with type 2 diabetes and healthy volunteers,[8] presumably because dietary fibers suppress absorption of carbohydrates from the intestine. In addition, dietary fiber suppresses lipid absorption from the intestine, thereby ameliorating obesity.9 In addition to dietary fibers, it is well documented that protein and lipid preload improves postprandial glucose excursion in individuals with type 2 diabetes and healthy volunteers through enhancement of secretions of insulin, GLP-1 and GIP.[10–12] Consistent with these findings, we have found that that consumption of fish or meat before rice improves postprandial glucose excursion by enhancing glucagon-like peptide-1 (GLP-1) and delaying gastric emptying in individuals with type 2 diabetes and healthy volunteers.[13] Considering these lines of evidence together, it is clear that consumption of meals with dietary fibers, protein and lipid before carbohydrate can improve postprandial glucose excursion. In fact, it has been shown that such meal sequence is effective in controlling postprandial glucose excursion in individuals with prediabetes as well as type 2 diabetes.[14–16] In addition, it is well known that GLP-1 enhances satiety and suppresses appetite, thereby ameliorating obesity. Thus, it is possible that eating vegetables with fish or meat before the staple, carbohydrate course can improve not only glycemia but also body weight in diabetes patients over the long term. Indeed, eating the vegetable and fish/meat course before the carbohydrate course has been shown to improve glycemic control and body weight in Japanese individuals with type 2 diabetes.[17] However, it is unknown whether such meal sequencing improves long-term glycemia and body weight in individuals with prediabetes.

Recently, a large-scale cross-sectional study among Japanese urban residents demonstrated that three dietary characteristics, “unhealthy food choices”, “overeating “and “irregular meal times” as well as sedentary behavior contribute independently to visceral fat accumulation. Nutritional balance in “unhealthy food choice” was characterized by lower protein/fat ratio, lower dietary fiber/carbohydrate ratio, and lower n-3 fatty acid/fat ratio.[18] Based on these observations, a dietary instruction program, SMART Washoku®, which can help individuals to consume diets with a higher protein/fat ratio, dietary fiber/carbohydrate ratio, and n-3 fatty acid/fat ratio was developed; its efficacy for behavioral modification among adults with normal glucose tolerance was demonstrated previously.[19] However, its efficacy among high-risk populations such as individuals with prediabetes has not yet been investigated.

This exploratory clinical trial examined the effects of dietary instructions focusing on meal sequence and nutritional balance in Japanese individuals with prediabetes in the national health check-up and guidance program.

2. Materials and methods

This was a multi-center, cluster-randomized, prospective, open-label, 3-arm parallel, comparative, exploratory study in Japanese individuals with prediabetes (UMIN-CTR clinical trial registration number: UMIN000027721). The protocol was approved by the ethics committee of Kansai Electric Power Medical Research Institute. The participants were recruited at five sites: Kansai Electric Power Co., Inc. (Osaka, Japan), Kanden Energy Solutions Co., Inc. (Osaka, Japan), Kanden Plant Corporation (Osaka, Japan), and Kanso Co., LTD. (Osaka, Japan). Since the current study was exploratory, the sample size was not set for hypothesis testing; 20 participants were expected in each site based on data from the last year's annual health checkup. The subjects were randomized using a prespecified computer-generated random number sequence into three groups as follows: Group A, receiving a conventional health guidance program; Group B, receiving health guidance with dietary instructions focusing on meal sequence; and Group C, receiving health guidance with dietary instructions focusing on nutritional balance using the Smart Washoku® program. Physicians, nurses and dieticians visited each site to conduct measurements on Visit 1 and Visit 3 and to give health guidance education on Visit 2. Written informed consent was obtained from all subjects.

2.1. Study participants and assessment

Male and female individuals who were enrolled in Kansai Electric Power Health Insurance, worked at one of the five sites, and required active support based on reports of annual health check-up were recruited. Those eligible were age 40–60 years and had no history of diabetes, fasting plasma glucose levels <126 mg/dL, HbA1c >5.6% (38 mmol/mol), and body mass index (BMI) 18–30 kg/m^2. Individuals with renal impairment, hepatic impairment, heart failure, history of cerebrocardiovascular disease, or gastro-intestinal surgery as well as those receiving glucose-lowering, blood pressure-lowering or lipid-lowering drugs were excluded. Subjects were excluded from the study if they had a diagnosis of diabetes in their health check-up within 3 months based on the diagnostic criteria of the Japan Diabetes Society.[20] Subjects were screened after informed consent at Visit 0 (week −4 to week 0). Those eligible were invited to receive physical assessment (i.e., body weight, waist circumference and estimated visceral fat area (VFA), blood pressure), blood sampling (i.e., HbA1c, fasting plasma glucose (FPG), 1,5-anhydroglucitol (AG)), and food frequency questionnaire (FFQ)-based dietary assessment[21,22] at Visit 1 (week 0) and Visit 3 (week 22–26). They also received health guidance education at Visit 2 (week 1–2) in accordance with the national health guidance program set by the Japanese Ministry of Health, without (Group A) or with (Group B and Group C) additional dietary instructions. In the national health guidance program, individuals receive a 6-month personalized lifestyle modification program, in which they are asked to adjust energy intake to balance the total energy expenditure and are encouraged to walk (e.g., “walk an extra 10 min whenever possible”).[23] Regarding dietary instruction, the subjects in Group A received dietary instruction focusing on energy expenditure. The subjects in Group B received dietary instruction focusing on meal sequence using a brochure, a place mat and a 5-min sandglass developed in the current study (details are available upon request). Briefly, participants were asked to ingest only foods without carbohydrate (i.e., salad, meat, fish) during the first 5 min, and were allowed to ingest foods with carbohydrate such as rice after a 5-min wait. The subjects in Group C received dietary instruction focusing on nutritional balance using the Smart Washoku® program developed by Kao Corporation, in which individuals are encouraged to increase protein intake, especially from fish and soy bean in place of fat; increase dietary fiber intake from vegetables, mushrooms, sea weeds, potatoes, beans and fruits; and increase the ratio of n-3 polyunsaturated fats in total fat intake.[24] All subjects were asked to wear pedometers to assess physical activity from Visit 1 to Visit 3. Each participant then was asked to report their adherence to their goals for diet and healthy exercise through e-mail every month from Visit 2 to Visit 3 using a scale of 1–5, where 1 indicated “seldom adhered” and 5 indicated “fully adhered”. The mean of monthly scores during the 6-month period was calculated for each participant. Recruitment of subjects began in June 2017 and the last follow-up date was December 2017.

2.2. Measurement

Glucagon was measured using Mercodia Glucagon ELISA (Catalogue 10-1271-01; Mercodia AB, Upsala, Sweden) according to the manufacture's instruction.[25] Insulin, GLP-1 and GIP were measured as described previously.[13] Insulin resistance and β-cell function were calculated according to the homeostasis model assessment (HOMA)

Table 1
Clinical parameters of participants before and 6 months after conventional health guidance (group a), health guidance with dietary instructions focusing on meal sequence (group b) or those with dietary instructions focusing on nutritional balance (group c).

		Group A (n = 11)				Group B (n = 18)				Group C (n = 13)				Repeated-measure ANOVA		
		Visit 1	Visit 3	Δ	P	Visit 1	Visit 3	Δ	P	Visit 1	Visit 3	Δ	P	Visit	Group	Visit*group
Age	(years)	52.7 ± 2.0	–	–	–	47.8 ± 1.1*	–	–	–	53.8 ± 2.4	–	–	–			
Bmi	(kg/m2)	25.6 ± 0.39	25.9 ± 0.50	0.32 ± 0.16	0.081	26.1 ± 0.59	26.0 ± 0.74	−0.17 ± 0.15*	0.320	25.7 ± 0.58	25.5 ± 0.64	−0.22 ± 0.30	0.468	0.001	0.816	0.079
Body weight	(kg)	75.7 ± 1.5	76.6 ± 1.6	0.90 ± 0.48	0.087	79.7 ± 2.2	79.2 ± 2.1	−0.53 ± 0.48*	0.289	75.7 ± 2.2	75.0 ± 2.4	−0.58 ± 0.87	0.521	0.001	0.303	0.074
Vfa	(cm2)	153.5 ± 5.5	140.9 ± 9.0	−12.6 ± 5.4	<0.05	159.2 ± 7.0	149.5 ± 5.8	−9.7 ± 4.1	<0.05	145.8 ± 8.2	132.3 ± 8.6	−13.5 ± 7.0	0.079	0.001	0.863	0.148
Wc	(cm)	95.1 ± 1.1	93.9 ± 1.5	−1.2 ± 0.9	0.205	96.7 ± 1.4	95.7 ± 1.2	−1.0 ± 0.7	0.148	95.1 ± 1.5	92.8 ± 1.8	−2.3 ± 0.9	<0.05	0.003	0.437	0.485
systolic bp	(mmhg)	130.5 ± 4.7	125.5 ± 4.4	−5.0 ± 4.1	0.250	132.2 ± 3.7	125.8 ± 3.2	−6.4 ± 3.4	0.077	130.2 ± 4.3	135.1 ± 4.1	−5.0 ± 3.1	0.140	0.308	0.490	0.620
diastolic bp	(mmhg)	87.6 ± 2.5	80.2 ± 3.4	−7.5 ± 2.6	<0.05	85.4 ± 2.9	82.8 ± 2.2	−3.7 ± 2.7	0.185	81.7 ± 2.1	88.3 ± 2.2#	6.6 ± 2.4*,#	<0.05	0.336	0.898	0.003
Fpg	(mg/dl)	111.0 ± 4.9	107.4 ± 5.5	−3.6 ± 2.4	0.154	115.6 ± 2.3	109.3 ± 2.9	−6.3 ± 1.9	<0.05	110.4 ± 2.9	105.0 ± 2.9	−5.4 ± 1.2	<0.05	0.000	0.551	0.621
1,5-ag	(μg/ml)	21.84 ± 2.83	20.71 ± 2.74	−1.13 ± 0.52	0.057	20.59 ± 2.20	20.42 ± 2.29	−0.17 ± 0.34	0.619	26.85 ± 2.08#	25.97 ± 2.10	−0.88 ± 0.58	0.153	0.011	0.173	0.309
Hba1c	(%)	6.00 ± 0.17	6.07 ± 0.15	0.07 ± 0.07	0.307	5.94 ± 0.08	5.99 ± 0.08	0.05 ± 0.04	0.252	5.87 ± 0.11	5.84 ± 0.08	−0.07 ± 0.04	0.307	0.281	0.517	0.315
Insulin	U/l	6.37 ± 0.93	6.60 ± 0.92	0.23 ± 0.66	0.737	8.33 ± 0.67	9.30 ± 0.74	0.97 ± 0.78	0.227	6.87 ± 0.82	5.90 ± 0.88#	−0.97 ± 0.56	0.110	0.875	0.028	0.153
Homa-ir		1.75 ± 0.28	1.80 ± 0.33	0.05 ± 0.18	0.812	2.37 ± 0.19	2.52 ± 0.21	0.15 ± 0.24	0.541	1.87 ± 0.23	1.51 ± 0.22#	−0.36 ± 0.16	<0.05	0.669	0.020	0.218
Homa-β		50.80 ± 7.56	59.02 ± 8.61	8.18 ± 7.47	0.299	59.90 ± 6.73	76.68 ± 8.16	16.82 ± 6.03	<0.05	55.70 ± 8.94	56.90 ± 12.48	1.20 ± 5.56	0.832	0.025	0.204	0.431
Total gip	Pmol/l	25.7 ± 4.6	25.6 ± 5.0	−0.0 ± 3.4	0.996	25.6 ± 4.1	24.1 ± 2.2	−1.5 ± 3.6	0.683	23.0 ± 3.2	22.3 ± 4.6	−0.7 ± 4.9	0.893	0.763	0.967	0.825
Total glp-1	Pmol/l	3.2 ± 0.5	3.2 ± 0.5	−0.1 ± 0.3	0.807	3.5 ± 0.4	3.5 ± 0.3	0.1 ± 0.3	0.764	3.4 ± 0.4	3.2 ± 0.4	−0.2 ± 0.2	0.286	0.667	0.842	0.698
Glucagon	Pmol/l	9.9 ± 1.1	9.9 ± 1.1	0.0 ± 0.7	0.992	10.4 ± 1.4	8.8 ± 1.2	−1.6 ± 1.0	0.125	9.8 ± 1.4	7.1 ± 1.1	−2.7 ± 0.5	<0.05	0.007	0.687	0.137
Ldl-chol	Mg/dl	123.4 ± 9.5	132.2 ± 8.7	8.8 ± 3.6	<0.05	128.9 ± 6.8	130.6 ± 8.1	1.7 ± 5.3	0.755	144.0 ± 8.8	135.7 ± 8.3	−8.3 ± 4.1*	0.067	0.799	0.544	0.074
Hdl-chol	Mg/dl	55.5 ± 4.2	56.4 ± 4.4	0.9 ± 2.0	0.659	50.8 ± 3.3	51.2 ± 3.2	0.4 ± 1.2	0.718	52.2 ± 3.7	52.8 ± 3.1	0.6 ± 1.2	0.618	0.441	0.975	0.627
Triglycerides	Mg/dl	136.1 ± 20.3	180.7 ± 44.9	44.6 ± 25.8	0.114	179.7 ± 21.7	207.4 ± 28.9	27.7 ± 20.5	0.193	154.9 ± 21.6	153.8 ± 25.4	−1.08 ± 18.7	0.955	0.070	0.461	0.378

All measurements were conducted after overnight fasting. AG, anhydroglucitol; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BP, blood pressure; chol, cholesterol; FPG, fasting plasma glucose; GLP-1, glucagon-like-peptide-1; GIP, glucose-dependent insulinotropic polypeptide; HDL, high density lipoproteins; HOMA, homeostasis model assessment; LDL, low density lipoprotein; VFA, visceral fat area; WC, waist circumference. Δ indicates values at Visit 3 – values at Visit 1. * and # indicate $p<0.05$ versus Group A and $p<0.05$ versus Group B, respectively.

model.[26] VFA was estimated by using multi-frequency bioelectrical impedance scales (EW-FA90, Panasonic Appliances Company, Tokyo, Japan). VFA was calculated using a value of waist circumference and a value of voltage occurring at the flank to the flow of current between the umbilicus and the back, as described previously.[27] The accuracy of the scale was demonstrated previously.[27] Other laboratory measurements including plasma glucose, HbA1c, and 1,5-AG were measured by standard assays.

2.3. Statistical analysis

Results were evaluated in the per-protocol set (PPS) population, which is identical to the full analysis set (FAS) population (Table 1 and Fig. 1). All analyses including repeated-measures ANOVA were performed using IBM SPSS Statistics 24 (IBM, Armonk, NY, USA). Values at Visit 1 and Visit 3 and changes at Visit 3 from Visit 1 were analyzed by paired *t*-test and unpaired t-test, respectively. Multiplicity was not adjusted as the current study was exploratory. Results are reported as mean ± SE unless otherwise stated. A two-sided *P* value <0.05 was taken to indicate significant difference.

3. Results

A total of 42 participants (Group A, $n = 11$; Group B, $n = 18$; Group C, $n = 13$) out of the 43 individuals screened were enrolled in the study (Table 1 and Fig. 1). One individual was excluded for being previously diagnosed with diabetes and being on anti-diabetic drugs. Baseline characteristics of the participants in Groups B and C, including FPG, 1,5-AG, and HbA1c as well as body weight, BMI, and VFA and waist circumference were similar to those of the participants in Group A (Table 1), although participants in Group B were 5–6 years younger than the other 2 groups ($p < 0.05$ for Group A vs B) (Table 1). All participants completed the interventions. Repeated-measure ANOVA analysis revealed some effects of visit x group interactions in BMI, body weight and low-density lipoprotein (LDL)-cholesterol, but they did not reach statistical significance (Table 1). Repeated-measure ANOVA analysis also demonstrated statistically significant effects of visit x group interactions in daily intake of n-3 polyunsaturated fat (PUFA), n-3 PUFA/total fat ratio, daily intake of dietary fiber, and some effects in daily intake of fat and saturated fat that did not reach statistical significance (Table 2).

3.1. Dietary instructions focusing on meal sequence

Body weight and BMI were reduced at Visit 3 from Visit 1 in Group B, while they were increased in Group A (Table 1). Changes of body weight and BMI were significantly different between Groups A and B. VFA and waist circumference were reduced at Visit 3 from Visit 1 in both groups, with statistical significance. Changes of visceral fat were comparable between the two groups. FPG levels were reduced at Visit 3 from Visit 1 in both groups, with statistical significance in Group B (Table 1). Changes of FPG at Visit 3 from Visit 1 were greater in Group B, although the difference did not reach statistical significance. 1,5-AG levels remained similar between Visits 1 and 3 in Group B, while they were substantially reduced in Group A. Change of 1,5-AG was less in Group B, although the difference did not reach statistical significance. HbA1c did not differ between Visits 1 and 3 in either group, and changes of HbA1c were comparable in the two groups.

Daily energy intake did not differ significantly between Groups A and B at Visit 1 (Table 2). Daily energy intake was decreased in Group B at Visit 3 from Visit 1, while it was increased in Group A. Changes of daily energy intake from Visit 1 to Visit 3 did not differ between Groups A and B. Proportions of carbohydrate, protein and fat of total energy intake did not differ at Visit 3 from Visit 1 in either group.

Adherence to goals for a healthy diet and achievement of goals for exercise were assessed on a scale of 1–5, where 1 indicated “seldom

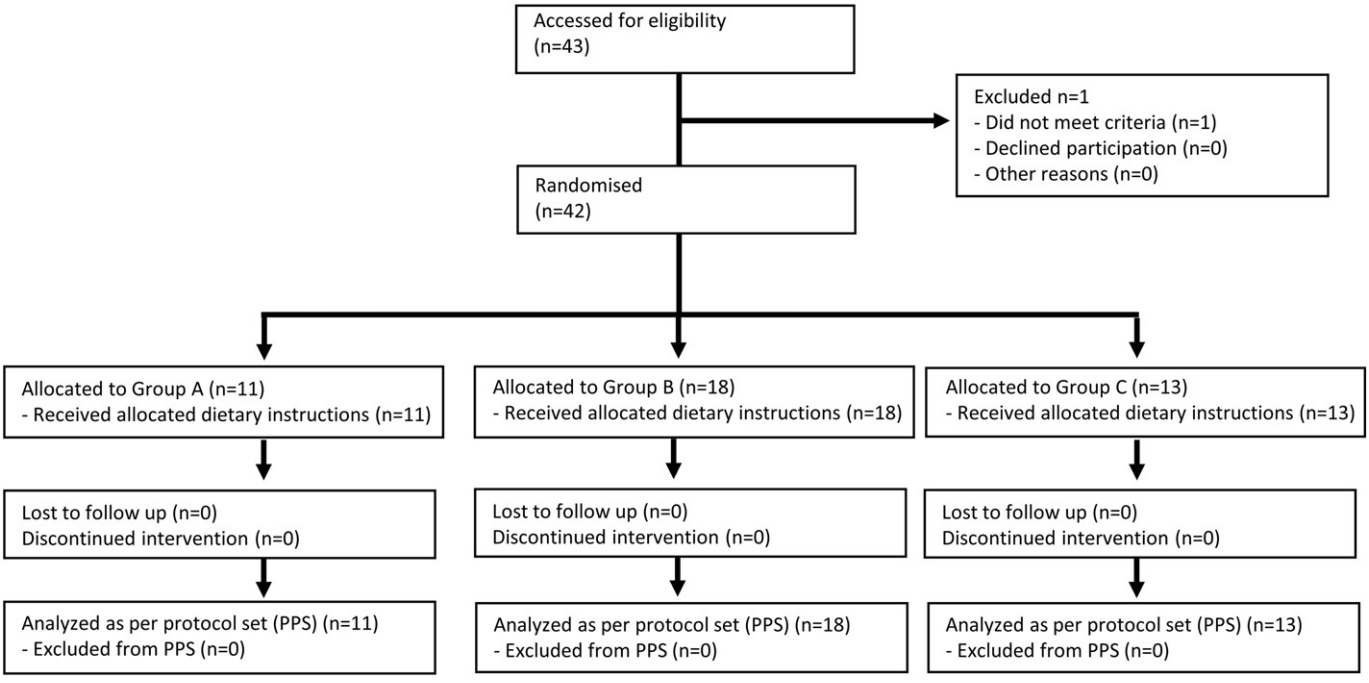

Fig. 1. Flow diagram of the study. Forty-three individuals were screened for this study. The subjects were cluster-randomized to three groups at Visit 1 (week 0): Those receiving conventional dietary instruction (Group A); those receiving dietary instruction focusing on meal sequence (Group B); and those receiving dietary instruction focusing on nutritional balance using the Smart Washoku® program (Group C) at Visit 2 (week 1–2). All subjects were followed for adherence to each of the dietary instructions by e-mail every month for 6 months. The participants received physical assessment (i.e., body weight, waist circumference, estimated visceral fat area, and blood pressure), blood sampling (i.e., HbA1c, fasting plasma glucose, 1,5-anhydroglucitol (AG)) and food frequency questionnaire (FFQ)-based dietary assessment at Visit 1 (week 0) and Visit 3 (week 22–26). All of the 42 individuals completed the study and were analyzed as the per-protocol set in the current study.

Table 2
Nutrition-related parameters of participants before and 6 months after conventional health guidance (Group A), health guidance with dietary instructions focusing on meal sequence (Group B) or those with dietary instructions focusing on nutritional balance (Group C).

		Group A (n = 11)				Group B (n = 18)				Group C (n = 13)				repeated-measure ANOVA		
		Visit 1	Visit 3	Δ	p	Visit 1	Visit 3	Δ	p	Visit 1	Visit 3	Δ	p	Visit	Group	Visit*group
Total energy intake	(kcal/day)	1846.7 ± 159.4	1892.2 ± 114.8	45.6 ± 120.6	0.714	1985.7 ± 105.3	1820.2 ± 88.8	−165.6 ± 87.0	0.074	1870.1 ± 85.2	1663.9 ± 90.3	−206.4 ± 113.8	<0.05	0.035	0.535	0.129
	(kcal/kg IBW/day)	28.1 ± 2.2	28.6 ± 1.4	0.5 ± 1.9	0.813	29.7 ± 1.6	27.3 ± 1.5	−2.4 ± 1.3	0.086	29.1 ± 1.4	25.8 ± 1.4	−3.4 ± 1.8	<0.05	0.027	0.798	0.139
Carbohydrate	(g/day)	228.3 ± 22.9	238.5 ± 15.0	10.3 ± 18.4	0.589	246.9 ± 15.2	226.7 ± 13.3	−20.2 ± 11.6	0.098	246.9 ± 11.8	223.0 ± 11.8	−23.9 ± 14.2	<0.05	0.103	0.966	0.150
	(%Energy)	48.8 ± 2.1	50.7 ± 1.7	1.8 ± 2.2	0.418	49.9 ± 1.6	49.6 ± 1.2	−0.3 ± 1.4	0.848	53.3 ± 2.0	54.0 ± 1.9	0.7 ± 1.9	0.491	0.353	0.183	0.651
Protein	(g/day)	61.3 ± 5.6	64.9 ± 5.2	3.6 ± 4.1	0.404	67.8 ± 3.9	61.6 ± 2.7	−6.2 ± 3.5	0.098	59.5 ± 3.6	53.6 ± 3.2#	−5.8 ± 4.2	0.096	0.149	0.215	0.137
	(%Energy)	13.3 ± 0.4	13.7 ± 0.6	0.3 ± 0.6	0.579	13.7 ± 0.4	13.7 ± 0.5	0.1 ± 0.5	0.884	12.7 ± 0.6	13.1 ± 0.9	0.4 ± 0.8	0.515	0.388	0.495	0.860
Fat	(g/day)	60.2 ± 5.3	62.9 ± 4.8	2.6 ± 4.0	0.528	65.2 ± 4.2	59.8 ± 3.6	−5.4 ± 2.8	0.175	59.2 ± 4.9	49.9 ± 4.1*,#	−9.4 ± 5.1*	<0.05	0.044	0.315	0.071
	(%Energy)	26.4 ± 1.2	26.4 ± 1.0	0.0 ± 1.6	0.983	26.1 ± 0.8	26.2 ± 0.8	0.1 ± 0.8	0.914	24.9 ± 1.3	23.7 ± 1.2	−1.2 ± 1.3	0.169	0.409	0.259	0.437
Protein/Fat	(%Energy /%Energy)	0.511 ± 0.018	0.520 ± 0.016	0.008 ± 0.020	0.695	0.533 ± 0.025	0.529 ± 0.019	−0.004 ± 0.023	0.866	0.522 ± 0.028	0.570 ± 0.050	0.048 ± 0.039	0.096	0.155	0.760	0.172
SFA	(g/day)	19.4 ± 1.9	19.2 ± 1.3	−0.23 ± 1.5	0.879	18.9 ± 1.4	17.9 ± 1.3	−1.0 ± 1.2	0.390	18.0 ± 1.5	14.5 ± 1.5*,#	−3.5 ± 1.6	<0.05	0.019	0.277	0.078
	(%Energy)	8.5 ± 0.5	8.1 ± 0.3	−0.3 ± 0.4	0.478	7.6 ± 0.3	7.8 ± 0.3	0.2 ± 0.3	0.521	7.6 ± 0.5	6.8 ± 0.5*	−0.8 ± 0.5	0.053	0.107	0.116	0.083
MUFA	(g/day)	21.9 ± 2.0	22.8 ± 1.9	0.8 ± 1.5	0.582	24.4 ± 1.6	22.3 ± 1.3	−2.1 ± 1.5	0.179	21.7 ± 2.0	18.2 ± 1.6*,#	−3.5 ± 2.0*	<0.05	0.043	0.262	0.118
	(%Energy)	9.6 ± 0.5	9.5 ± 0.5	−0.0 ± 0.6	0.978	9.8 ± 0.4	9.8 ± 0.3	−0.0 ± 0.4	0.991	9.1 ± 0.5	8.6 ± 0.5	−0.5 ± 0.5	0.150	0.350	0.229	0.453
PUFA	(g/day)	12.2 ± 0.9	13.9 ± 1.2	1.7 ± 0.9	0.084	14.7 ± 1.1	13.1 ± 0.8	−1.6 ± 1.0*	0.124	12.7 ± 1.1	11.6 ± 0.8	−1.2 ± 1.2*	0.122	0.332	0.398	0.049
	(%Energy)	5.5 ± 0.3	5.8 ± 0.3	0.4 ± 0.5	0.513	5.8 ± 0.3	5.7 ± 0.2	−0.1 ± 0.3	0.677	5.4 ± 0.3	5.6 ± 0.3	0.2 ± 0.3	0.768	0.573	0.606	0.645
n^{-3} PUFA	(g/day)	2.0 ± 0.2	2.4 ± 0.2	0.3 ± 0.2	0.213	2.5 ± 0.2	2.2 ± 0.1	−0.3 ± 0.2	0.162	2.1 ± 0.2	2.1 ± 0.1	0.0 ± 0.2	0.591	0.844	0.460	0.105
n-3 PUFA/total fat	(g/g)	0.035 ± 0.002	0.038 ± 0.001	0.003 ± 0.003	0.338	0.038 ± 0.001	0.037 ± 0.002	−0.001 ± 0.002	0.705	0.035 ± 0.002	0.044 ± 0.004	0.008 ± 0.003	<0.05	0.015	0.344	0.018
Cholesterol	(mg/day)	332.6 ± 38.3	322.9 ± 32.2	−9.6 ± 18.6	0.617	306.9 ± 21.5	298.4 ± 22.6	−8.5 ± 19.4	0.667	333.6 ± 28.1	290.9 ± 20.3	−42.7 ± 32.8	0.083	0.063	0.738	0.219
Dietary fiber	(g/day)	10.0 ± 0.9	11.7 ± 1.2	1.7 ± 0.9	0.083	12.3 ± 1.0	10.9 ± 0.7	−1.3 ± 0.9*	0.148	10.4 ± 0.4	10.0 ± 0.6	−0.3 ± 0.5	0.476	0.990	0.289	0.044
Dietary fiber/carbohydrate	(g/g)	0.047 ± 0.005	0.049 ± 0.004	0.002 ± 0.006	0.722	0.050 ± 0.002	0.050 ± 0.004	0.000 ± 0.004	1.000	0.043 ± 0.002	0.046 ± 0.004	0.003 ± 0.003	0.224	0.422	0.302	0.784
Salt	(g/day)	9.1 ± 0.7	9.8 ± 0.8	0.7 ± 0.8	0.375	8.8 ± 0.7	8.9 ± 0.6	0.1 ± 0.6	0.896	9.4 ± 0.6	9.8 ± 1.0	0.3 ± 1.0	0.522	0.275	0.792	0.773

PUFA, polyunsaturated fat; MUFA, monounsaturated fat; SFA, saturated fat. * and # indicate $p<0.05$ versus Group A and $p<0.05$ versus Group B.

adhered" and 5 indicated "fully adhered" through e-mail every month from Visit 2 to Visit 3; the means of monthly scores during the 6-month period were calculated for each participant, and were compared between the two groups (Table 3). Achievement of goals for healthy diet and exercise did not differ between Groups A and B. The number of daily steps did not differ between the two groups (Table 3).

3.2. Dietary instructions focusing on nutritional balance

Body weight and BMI were reduced at Visit 3 from Visit 1 in Group C but not in Group A (Table 1), although body weight and BMI did not differ significantly between the two groups. VFA was reduced at Visit 3 from Visit 1, with statistical significance in Group A but not in Group C. Changes in VFA did not differ between Groups A and C. Waist circumference was decreased at Visit 3 from Visit 1 in both groups, with statistical significance in Group C. FPG levels were reduced at Visit 3 from Visit 1 in both groups, with statistical significance in Group C (Table 1). Changes of FPG at Visit 3 from Visit 1 were greater in Group C, although the difference did not reach statistical significance. 1,5-AG levels were reduced at Visit 3 from Visit 1 similarly in the two groups, suggesting increased postprandial glucose elevation in both Groups. HbA1c did not differ between Visit 3 and Visit 1 in either group. Changes of FPG, HbA1c, and 1,5-AG from Visit 1 to Visit 3 did not differ between Groups A and C.

Daily energy intake did not differ significantly between Groups A and C at Visit 1 (Table 2). Daily energy intake was decreased at Visit 3 from Visit 1, with statistical significance in Group C, while it was increased in Group A. Changes of daily energy intake from Visit 1 to Visit 3 did not differ between the two Groups. Proportions of carbohydrate, protein and fat in total energy intake did not change at Visit 3 from Visit 1 in either group. However, the ratio of n-3 polyunsaturated fats and total fats was significantly increased in Group C.

Achievement of goals for a healthy diet was significantly lower in Group C compared to Group A, suggesting that dietary instructions focusing on nutritional balance were difficult to observe by the participants. Achievement of goals for exercise did not differ between Groups A and C (Table 3). The number of daily steps did not differ between Groups A and C (Table 3).

Changes of each parameter, except for diastolic blood pressure, from Visit 1 to Visit 3 in Table 1 did not differ between Groups B and C (Table 1). Changes of daily energy intake as well as daily carbohydrate, protein and fat intake from Visit 1 to Visit 3 did not differ between Groups B and C (Table 2). Achievement of goals for a healthy diet was significantly lower in Group C compared to Group B. Achievement of goals for exercise did not differ between Groups B and C (Table 3). The number of daily steps did not differ between Groups B and C (Table 3).

Table 3
Adherence to healthy diet and exercise of participants after conventional health guidance (Group A), health guidance with dietary instructions focusing on meal sequence (Group B) or those with dietary instructions focusing on nutritional balance (Group C).

	Group A (n = 11)	Group B (n = 18)	Group C (n = 13)
Adherence to healthy diets	3.6 ± 0.2	3.5 ± 0.2	2.9 ± 0.2*, #
Adherence to exercise	3.3 ± 0.2	3.5 ± 0.1	3.1 ± 0.2
Daily steps (steps/day)	8967 ± 599	8796 ± 720	10,147 ± 729

All subjects were asked to set one goal for a healthy diet (e.g., "adjust total energy intake to balance total energy expenditure") and one for healthy exercise (e.g., "Walk an extra 10 min whenever possible") after health guidance education at Visit 2. Specifically, subjects in Group B and Group C were asked to set "Observe meal sequence" and "Use Smart Washoku® program" as a goal for a healthy diet, respectively. Each participant then was asked to report their adherence to their goals for diet and healthy exercise through e-mail every month from Visit 2 to Visit 3 using a scale of 1–5, where 1 indicated "seldom adhered" and 5 indicated "fully adhered". The mean of monthly scores during the 6-month period was calculated for each participant. Values for adherence to healthy diet, exercise and daily steps indicate means ± SE. * and # indicate $p<0.05$ versus Group A and $p<0.05$ versus Group B.

4. Discussion

In the current cluster-randomized, prospective, exploratory study in Japanese individuals with prediabetes, we found that dietary instructions focusing on meal sequence produced a greater reduction in body weight than that in the study group receiving conventional instructions, with similar adherence, while the effects on glycemia did not differ between the two study groups. We also found that dietary instructions focusing on nutritional balance were effective in reducing body weight, although adherence was significantly lower than that in the study group receiving conventional instructions.

Changes of body weight and BMI were significantly greater in Group B, which received dietary instructions focusing on meal sequence, when compared to Group A, which received conventional dietary instructions. Possible explanations of this finding include subjects in Group B being slightly more obese and so might more readily lose body weight in response to dietary instructions. It is also reasonable to consider the anorectic action of GLP-1. We have previously demonstrated that consumption of fish or meat before carbohydrate enhances postprandial secretion of GLP-1.[13] It is well known that GLP-1 enhances satiety and suppresses appetite, thereby reducing body weight.[28] Although postprandial GLP-1 levels were not determined in the current study, it is likely that the dietary instructions focusing on meal sequence reduced body weight through such GLP-1 actions. Indeed, the FFQ revealed that daily energy intake was reduced in Group B by 165.6 ± 87.0 kcal/day at Visit 3 from Visit 1, while it was increased in Group A by 45.6 ± 120.6 kcal/day. It is also possible that carbohydrate-last meal intervention lowers postprandial insulin peaks, thereby contributing to body weight loss, as previously proposed.[29] Although the increases in body weight suggest poor adherence to nutritional and lifestyle interventions in all 3 groups, the participants completed their follow-up period during the winter months when Japanese generally tend to gain body fat due to increased food intake and reduced exercise.[30]

Previous studies demonstrated that consumption of fish or meat and vegetable before carbohydrate ameliorated postprandial glucose excursions.[8,13] While changes of FPG were larger and those of 1,5-AG were smaller in Group B than in Group A, the current study failed to demonstrate significant improvement of glycemia by dietary instructions focusing on meal sequence. This may be due to several reasons including: 1) Prediabetes in the current study included both individuals with impaired glucose tolerance (IGT) and those with impaired fasting glucose (IFG), and carbohydrate-last meal sequence may exert greater glucose-lowering effects in those with IGT than IFG, 2) e-mail-based monthly evaluation might have overestimated adherence to dietary instructions focusing on meal sequence, and 3) as dietary instruction focusing on meal sequence has been introduced in Japan though TV programs in the past few years, it is possible that some of the participants in Groups A and C used meal sequencing without such education at Visit 2.

Changes of body weight and BMI were greater in Group C, which received dietary instructions focusing on nutritional balance, when compared to Group A, which received conventional dietary instructions. It has been demonstrated that the SMART Washoku® program reduced body weight, BMI, and waist circumference and VFA in prospective, single-arm, observational study.[19] Indeed, FFQ revealed that daily energy intake was reduced in Group C by 206.4 ± 113.8 kcal/day at Visit 3 from Visit 1, while it was increased in Group A by 45.6 ± 120.6 kcal/day, and that the n-3 polyunsaturated fat/total fat ratio was significantly increased at Visit 3 from Visit 1 in Group C but not in Group A, which suggests a possible contribution of the significant reduction of LDL-c. One of the surprises related to the SMART Washoku® program in this study was the lower achievement of goals for a healthy diet in Group C compared to Group A. In fact, changing and keeping nutritional balance in daily diet has been shown in the past to be very difficult, and our previous study demonstrated that repeated SMART Washoku® programs were more effective among healthy individuals.[19] Thus, it would

be interesting to see if repeated, not one time only, face-to-face instructions improved the effects of the SMART Washoku® program in individuals with prediabetes. Diastolic blood pressure was unexpectedly increased in Group C, while diastolic blood pressure in Group A and Group B and systolic blood pressure in all 3 groups were decreased from Visit 1 to Visit 3 (Table 1). The mechanisms underlying this change are unknown, and it remains to be seen if it can be reproduced.

The daily protein intake was relatively low (approx. 13% energy) (Table 1). While the recent consensus report from the American Diabetes Association describes that individuals with diabetes, on average, eat about the same proportion of macronutrients as the general public: ~45% of their calories from carbohydrate, ~36–40% of calories from fat, and the remainder (~16–18%) from protein, there is no ideal mix that applies broadly and macronutrient proportions should be individualized.[31] The current dietary reference intakes for Japanese set ideal proportions of macronutrients for the general public as ~50–65% of their calories from carbohydrate, ~20–30% of calories from fat, and the remainder (~13–20%) from protein[32]; the Japan Diabetes Society's guidelines recommend ideal proportions of macronutrients for individuals with diabetes as ~50–60% of their calories from carbohydrate, 20% or less of calories from protein, and the remainder (~20–30%) from fat.[33,34] The low daily protein intake in the current study (approx. 13%) might be partly explained as influence by these Japanese guidelines.

Limitations of the current study include 1) Assessment of adherence to dietary instructions depended on FFQ, which does not evaluate dietary habits such as meal sequence or participants' responses to monthly questionnaires. Thus, it might overestimate adherence to dietary instructions focusing on meal sequence. 2) Face-to-face dietary instructions were conducted one time only, which makes it difficult to fully communicate the SMART Washoku® program. 3) The sample size was smaller than planned, and some baseline parameters were not comparable among the three groups. However, since participants were recruited based on their annual medical check-up reports, it was difficult to increase the sample size by extending the recruiting period. Nevertheless, this exploratory study suggests the feasibility and likely efficacy of adding dietary instructions focusing on meal sequence to the conventional dietary instructions in the national health check-up and guidance program in Japan.

In conclusion, we found in the current cluster-randomized, prospective, exploratory study in Japanese individuals with prediabetes that health guidance with dietary instructions focusing on meal sequence had similar adherence and was more effective in reducing body weight than conventional health guidance.

Declaration of competing interest

D. Yabe received consulting or speaker fees from MSD K.K., Novo Nordisk Pharma Ltd. and Nippon Boehringer Ingelheim Co., Ltd. D. Yabe also received clinical commissioned/joint research grants from Nippon Boehringer Ingelheim Co., Ltd., Eli Lilly and Company, Taisho Toyama Pharmaceutical Co. Ltd., MSD K.K., Ono Pharmaceutical Co. Ltd., Novo Nordisk Pharma Ltd., Arklay Co. Ltd., Sanofi K.K., Astellas Pharma Inc. and Takeda Pharmaceutical Company Limited. Y. Hamamoto received consulting or speaker fees from Novo Nordisk Pharma Ltd. T. Kurose received consulting or speaker fees from Sanofi K.K. T. Kurose also received clinical commissioned/joint research grants from the Japan Vascular Disease Research Foundation. Yut. Seino received consulting or speaker fees from Eli Lilly Japan K.K., Sanofi K.K., Novo Nordisk Pharma Inc., Glaxo-Smith-Kline, Taisho Pharmaceutical Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., Astellas Pharma Inc., BD, Nippon Boehringer Ingelheim Co., Ltd., Johnson & Johnson and Takeda Pharmaceutical Company Limited. Yut. Seino also received clinical commissioned/joint research grants from Nippon Boehringer Ingelheim Co., Ltd., Eli Lilly and Company, Taisho Toyama Pharmaceutical Co. Ltd., MSD K.K., Ono Pharmaceutical Co. Ltd., Novo Nordisk Pharma Ltd., and Arklay Co. Ltd. H. Kuwata, Y. Fujiwara, K. Murotani, M. Sakaguchi, S. Moyama, N. Makabe, Yus. Seino, H. Asano, S. Ito and H. Mishima report no conflict of interest relevant to this study. H. Takase and N. Oota are employees of Kao Corporation.

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Contribution statement

D. Yabe and Yut. Seino contributed to the conception and design of the research and the analysis, interpretation of data and writing of the manuscript. K. Murotani contributed to the statistical analysis and interpretation of data and the writing of the manuscript. H. Kuwata, S. Moyama, M. Sakaguchi, S. Moyama, N. Makabe, H. Asano, S. Ito, H. Mishima, H. Takase, N. Ota, Yus. Seino, Y. Hamamoto, and T. Kurose contributed to the analysis and interpretation of data and critical revisions of the manuscript for important intellectual content. All authors approved the version to be published. D. Yabe and Yut. Seino are the guarantors of this work.

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