J Rehabil Health Sci 2010; **8**: 1-7

Review

Eating Order Diet Reduced the Postprandial Glucose and Glycated Hemoglobin Levels in Japanese Patients with Type 2 Diabetes

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Received September 2, 2010 ; accepted September 29, 2010

Key words : type 2 diabetes; dietary interventions; glycemic control; vegetables; carbohydrate

1 Postprandial hyperglycemia is associated with increased risk for macrovascular diseases

It is important to manage good metabolic control in patients with diabetes in order to prevent chronic complications.[1,2] However, a significant number of patients with diabetes remain poorly controlled, mainly as a result of low compliance of diet.[3-5] The important choices that affect blood glucose control in people with diabetes are made by themselves, and not by their physicians or other medical professionals. People with diabetes are advised to adopt an appropriate diet including dietary habits and meal patterns on a lifelong basis. Frequently, the efforts of patients are not in the appropriate directions, or they may receive confusing and contradictory advice from the media or social contacts. Diabetes education, especially dietary education, requires training by medical professionals and provision of unequivocal information. Traditionally, recognition of the relationship between dietary constituents and glucose tolerance has contributed to the development of nutritional prescriptions. Such strategies aim to restrict energy intake and provide macronutrient balance. However, diabetic patients may have trouble understanding diets based on a restrict energy intake, and even if they do understand the system, they may have difficulty changing their daily food habits.[3] In particular, elderly diabetic patients may experience difficulties implementing the recommendations of the restrict energy intake.

It has been demonstrated that postprandial hyperglycemia is associated with increased risk for macrovascular diseases.[6] The recommendations of the International Diabetes Federation in 2007 were intended to assist in developing strategies to effectively manage postprandial glucose levels in people with diabetes. Strategies for nutritional education should be re-organized to provide a simple and easy meal plan that lowers postprandial hyperglycemia in patients with diabetes.

First, we reported an acute study of eating 'vegetables before carbohydrate' on postprandial glucose and insulin levels in patients with type 2 diabetes mellitus (T2DM). Second, we analyzed the retrospective study to determine whether educating diabetic patients to eat 'vegetables before carbohydrate' was effective on long-term glycemic control.

2 Crossover study of the effect of 'vegetables before carbohydrate' on the postprandial glucose and insulin levels in Japanese patients with type 2 diabetes mellitus[7]

We conducted a randomized crossover study in subjects with T2DM. We recruited 15 patients (7 men and 8 women), enrolled from outpatients with T2DM controlled by diet in Kajiyama Clinic specializing in the diabetes treatments. The exclusion criteria were as follows: (1) mean hemoglobin A1c (HbA1c) level in the past 6 months > 6.9% (2) chronic liver disease or a clinical history and/or signs of cardiovascular disease, cerebrovascular disease, or peripheral arterial disease (3) heavy smoking (more than 40 cigarettes a day), and drinking (more than 50 g alcohol a day); (4) and use of any dietary supplement in the 2 months before the start of the study. No change was made to therapy during the study.

Their clinical characteristics were as follow, mean ± SD; age 61.7 ± 11.6 yrs, BMI 24.7 ± 4.3 kg/m^2, HbA1c 6.0 ± 0.6%, duration of T2DM 5.3 ± 8.8 yrs. A test meal,

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consisted of white rice and vegetable salad of sliced cabbage and tomato, contains total energy of 340 kcal with 61.8 g of carbohydrate, 7.7 g of fat, 4.8 g of protein, and 1.9 g of fiber. Subjects ate test meals consisting of white rice and vegetable salad, eating either 'vegetables before carbohydrate' or vice versa for 4 weeks. On each test day, patients came to the clinic at 8:45 in the morning after a 12-hour overnight fast. After being weighed and having a fasting blood sample obtained, the patients consumed the test meals either eating rice first or vegetables first, chewing more than 20 times each bite with a 10-min interval between rice and vegetables (Fig.1). Further blood samples were obtained at 30, 60, and 120 minutes after the end of the meal. Plasma glucose and insulin levels were evaluated at each test meal. The subjects were instructed to maintain low physical activity throughout the following 2 h of blood sampling. The study protocol was approved by the Ethics Committee of the School of Comprehensive Rehabilitation at Osaka Prefecture University and all participants gave written informed consent prior to enrollment in the study. No changes were made to antihypertensive and lipid-lowering therapies during the study in all groups.

No significant differences were found between mean fasting blood glucose or insulin values in two of the test days. Time course of plasma glucose and insulin levels after consumption of the test meal in each test day were shown in Fig.2. Postprandial plasma glucose levels of eating vegetables before carbohydrates were reduced at 30 and 60 minutes compared to eating rice before vegetables (Fig. 2A). Additionally, postprandial plasma insulin levels of eating 'vegetables before carbohydrate' showed a significant decreased at 30 and 60 minutes compared to eating rice before vegetables (Fig. 2B). There was no significant difference in postprandial plasma glucose levels at 120 minutes between each test day.

In this study, for the first time, we demonstrated that the effect of consuming vegetables before rice on reducing the postprandial glucose and insulin levels in subjects with T2DM. These results suggest that eating vegetables before carbohydrate may be beneficial for subjects with postprandial hyperglycemia and T2DM.

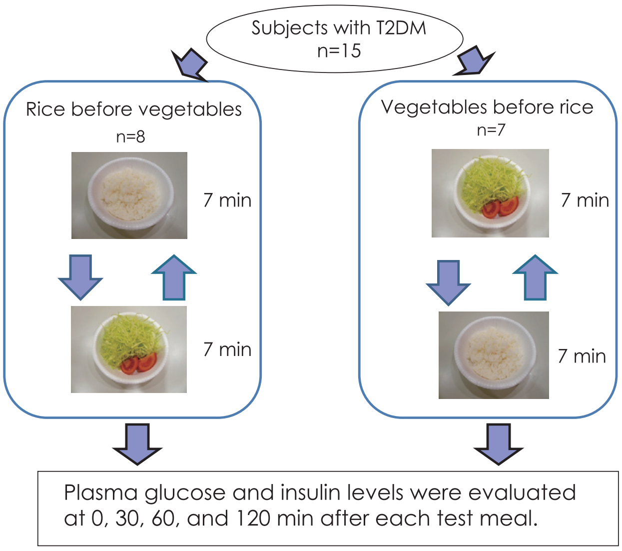

Fig. 1 Study protocol of crossover study of eating order diet.

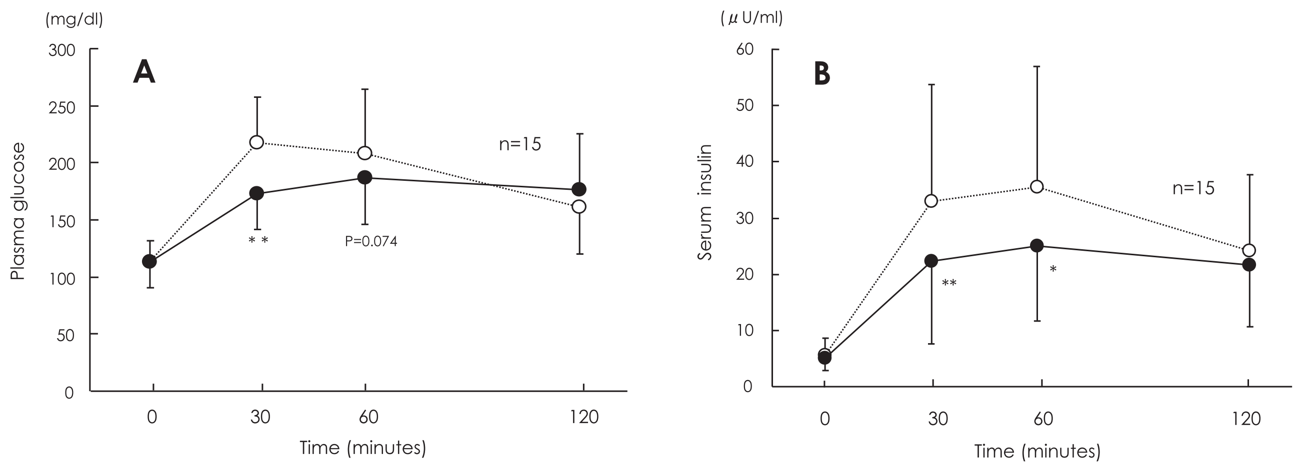

Fig. 2 Time course of (A) plasma glucose or (B) serum insulin at 0, 30, 60 and 120 minutes after eating rice before vegetables (○) or the reverse regimen (●) (n = 15). Plasma glucose at 30 minutes after eating vegetables before rice was significantly reduced compared to the reverse regimen ($p < 0.01$). Serum insulin at 30 and 60 minutes after following the same regimen ($p < 0.01$) was also significantly reduced compared to the reverse regimen ($p < 0.05$). Data is expressed as mean ± SD. * $p < 0.05$, ** $p < 0.01$, rice first vs. vegetables first. Cited from Imai S et al. (2010) J Japan Diab Soc, 53: 112-115

3 Retrospective study of the effect of eating 'vegetables before carbohydrate' on long-term glycemic control in Japanese patients with type 2 diabetes[8]

In addition to lowering acute postprandial glucose and insulin responses, we evaluated the study to determine whether educating diabetic patients to eat 'vegetables before carbohydrate' was effective on long-term glycemic control. To test this hypothesis, we carried out a retrospective study in patients with T2DM that compared changes in HbA1c as the primary outcome and changes in weight, serum lipids, and blood pressure as the secondary outcomes.

A total of 333 in 672 outpatients with T2DM in Kajiyama Clinic were selected for possible participation in the study if they had no major complications or medical illnesses. The protocol was approved by the Ethics Committee of the School of Comprehensive Rehabilitation at Osaka Prefecture University. Informed consent was obtained from all the subjects. The patients were divided into two groups to receive instructions on a simple meal plan of eating 'vegetables before carbohydrate' (educational group, n = 196) without taking into account of energy intake, or a control group (n = 137) of taking medical examination by a doctor. All patients were scheduled for return visits at every 4 weeks with physical examination and patients in the educational group were routinely scheduled to see dietitians at every visit. Dietary practices and physical activity were assessed in educational group.

The method of the education included nutritional advice given in the form of a simple and easy meal plan of eating 'vegetables before carbohydrate'. In order to reduce postprandial hyperglycemia, patients in the educational group were encouraged to consume every meal eating vegetables prior to carbohydrate and chewing each bite more than 20 times. Depending on the patient's current dietary intake, the intervention aimed to encourage increased consumption of vegetables, mushrooms, and seaweeds using an original educational brochure (Fig. 3). The intervention focused on setting individual and realistic goals in order to achieve gradual dietary changes. Approximately 30 minutes were spent on dietary counseling at the initial visit and 20 minutes at each subsequent session. Dietary intake was assessed by food records collected over three days at the initial visit (baseline) and over seven days after 2 months of the intervention. The dietitians were trained in all aspects of instruction and coping skills, which include planning menu and making appropriate food choices. Instructions for the education regarding diet involved the same dietitian each time.

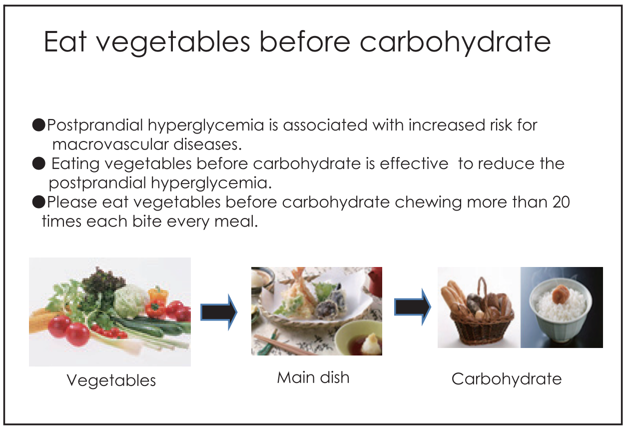

Fig. 3 The educational brochure of eating vegetables before carbohydrate for the patients with T2DM.

The dietary values were entered into a computer database and analyzed by a dietitian, using a dietary program (Eiyokun, Kenpakusha, Tokyo, Japan). Physical activity involving moderate exercise such as walking 30 to 40 minutes each day was recommended, and assessed in both groups using Kens Activity Monitor Life Corders® (Suzuken, Aichi, Japan) for 7 days prior to intervention and 21 days after intervention. Dietary restraint and overeating tendencies, such as emotional and external eating were measured using the Dutch Eating Behavior Questionnaire (DEBQ).[9] The patients were required to complete the DEBQ at the initial visit and after 2 months of intervention. Emotional eating was defined as eating in response to states of emotional arousal such as fear, anger or anxiety, while external eating was classified as eating in response to external food cues such as the sight and the smell of food or eating in response to food-related stimuli. Restrained eating was defined as overeating after a period of slimming when the cognitive resolve to diet was abandoned.

The control group involved the patients receiving their usual outpatient management every 4 weeks. The patients in the control group were given general information about lifestyle and diabetes risk by either a doctor or nurse at every visit.

At baseline, the educational group and the control group were comparable in sex, BMI and HbA1c, although there were significant differences between the two groups for mean age, duration of diabetes, systolic blood pressure, and percentage of each therapy (Table 1). As illustrated in Fig. 4, HbA1c levels decreased significantly soon after intervention and over the 30-month follow-up period in the educational group. Improvements in HbA1c levels over 30 months were observed from 8.3 to 7.1%

Table 1 Characteristics of the patients in study groups

	Educational group (n = 196)	Control group (n = 137)	*p*
Male/female (n)	99 / 97	62 / 75	0.345
Age (years)	62.8 ± 11.8	67.1 ± 9.3	< 0.001
BMI (kg/m^2)	24.2 ± 4.9	24.2 ± 4.0	0.758
Duration of DM (years)	7.1 ± 8.0	12.4 ± 9.2	< 0.001
SBP (mmHg)	132 ± 17	138 ± 16	< 0.001
DBP (mmHg)	76 ± 11	75 ± 10	0.339
HbA1c (%)	8.2 ± 1.8	7.8 ± 1.5	0.133
Total cholesterol (mg/dl)	215 ± 37	210 ± 34	0.197
LDL cholesterol (mg/dl)	131 ± 33	124 ± 29	0.059
HDL cholesterol (mg/dl)	58 ± 16	57 ± 14	0.736
Triglyceride (mg/dl)	142 ± 83	140 ± 89	0.869
Therapy			
Diet only	55	6	< 0.001
OHA	111	94	0.018
Insulin	2	8	0.014
Insulin + OHA	28	29	0.068

Data is expressed as mean ± SD, or n.
OHA; Oral hypoglycemic agents

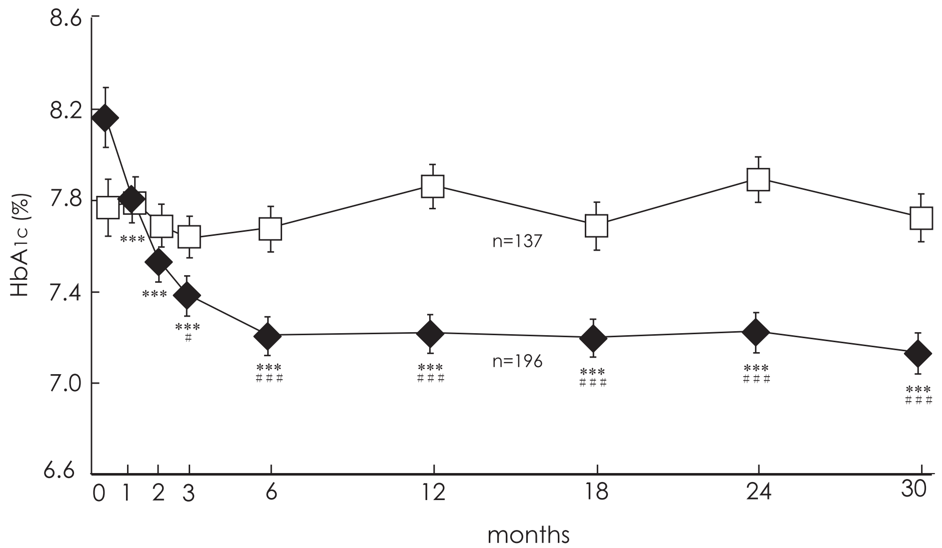

Fig. 4 Changes in mean HbA1c levels in patients in the educational group (◆) and the control group (□) over the 30-month follow-up period. Data is expressed as mean ± SE. Significant difference from baseline, *** $p < 0.001$. Educational group vs. control group; # $p < 0.05$, ### $p < 0.001$.

with the educational group ($p < 0.001$) while no change was observed with the control group, from 7.8 to 7.7%, and the values in the educational group were significantly lower than the control group after 3 to 30 months of study period. The improvements of glycemic control were observed in patients of the educational group whether therapies or duration of DM after the intervention. The levels of blood pressure, total cholesterol, and LDL cholesterol decreased significantly in both groups after 12 or 30 months (Table 2). Patients in the educational group had a greater reduction in systolic blood pressure at both 12 and 30 months and showed higher HDL cholesterol after 30 months compared to the control group. On the other hand, the diastolic blood pressure demonstrated a slight reduction in the control group after 30 months of the intervention.

After the intervention, dietary energy intake, protein, fat and carbohydrate were decreased in the educational

Table 2 BMI, blood pressure , and serum lipids in study groups after the intervention

	Educational group (n = 196)		Control group (n = 137)	
	after 1 year	after 2.5 years	after 1 year	after 2.5 years
BMI (kg/m^2)	24.1 ± 5.3	22.9 ± 7.2**	24.4 ± 3.8	23.6 ± 5.3
SBP (mmHg)	125 ± 11***	127 ± 12***	128 ± 12***	127 ± 10***
DBP (mmHg)	72 ± 9***	71 ± 8***	70 ± 8***	70 ± 8***†††
Total cholesterol (mg/dl)	202 ± 36***	200 ± 36***	201 ± 36*	195 ± 38***
LDL cholesterol (mg/dl)	121 ± 32***	117 ± 33***	117 ± 26*	113 ± 30**
HDL cholesterol (mg/dl)	59 ± 15	60 ± 17*††	57 ± 13	55 ± 14*
Triglyceride (mg/dl)	132 ± 76	127 ± 74*	153 ± 113	148 ± 117

Data is expressed as mean ± SD.
Baseline vs. after 1 year or 2.5 years; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$
Educational group vs. control group; $^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$, $^{\dagger\dagger\dagger}p < 0.001$

Table 3 Dietary intakes of before and after the intervention in the educational group

		before	after	*p*
Dietary intakes				
Energy	kcal	2,473 ± 143	1,712 ± 43	0.000
Protein	g	81.9 ± 3.8	72.5 ± 2.4	0.024
Fat	g	72.8 ± 6.0	48.4 ± 1.9	0.001
Carbohydrate	g	335 ± 24	229 ± 8	0.000
Fiber	g	14.9 ± 0.8	18.1 ± 0.6	0.054
Salt	g	11.8 ± 0.6	9.5 ± 0.3	0.000
Intake of food groups				
Grains	g	462 ± 40	357 ± 22	0.025
Potatoes	g	46.7 ± 14.6	50.7 ± 9.6	0.823
Sugar	g	14.2 ± 2.8	7.2 ± 1.1	0.019
Nuts	g	2.8 ± 1.2	2.7 ± 1.2	0.957
Green vegetables	g	93 ± 16	199 ± 22	0.000
Other vegetables	g	194 ± 17	310 ± 36	0.007
Mushrooms	g	18.6 ± 10.7	18.9 ± 5.4	0.982
Sea weeds	g	9.4 ± 2.2	5.2 ± 1.6	0.144
Fruits	g	139 ± 25	80 ± 24	0.046
Beans	g	64 ± 16	81 ± 15	0.482
Fish	g	86 ± 13	103 ± 13	0.341
Meat	g	89 ± 13	58 ± 9	0.085
Egg	g	35 ± 6	31 ± 6	0.511
Milk	g	85 ± 17	71 ± 16	0.454
Oil	g	20 ± 3	12 ± 4	0.029
Sweets	g	49 ± 10	14 ± 4	0.001
Beverage	g	421 ± 68	267 ± 58	0.002

Data is expressed as mean ± SE.

group (Table 3). These reductions of dietary nutrients were the results of the decrease of the consumption of grain (rice), fruits, oil, sweets and beverages. On the other hand, consumption of vegetables increased after intervention in the educational groups with a significant increase in consumption of green vegetables. The energy expenditure and eating behavior assessed by the DEBQ demonstrated improved in the educational group after intervention.

4 Re-organize the nutritional strategies for helping diabetic patients adhere to dietary regimens

Patients with diabetes encounter several psychological and lifestyle difficulties in modifying their lives to achieve diabetic management.[10] They exhibit restrictive behaviors with regards to food intake and are convinced that rigid dietary control is the only way to obtain good glycemic control. The approach of eating ‘vegetables before carbohydrate’ was easier to understand and teach than other approaches. The most important aspect was also easier to attain by making the appropriate behavioral changes for participants. Our initial hypothesis that the education of eating ‘vegetables before carbohydrate’ would result in a more favorable dietary regimen for participants. In this study, we demonstrated that the effect of consuming vegetables before rice on the reduction of the postprandial glucose and insulin levels in subjects with T2DM. In addition to lowering acute postprandial glucose and insulin responses, our results support the hypothesis that educating patients with T2DM to eat ‘vegetables before carbohydrate’ was effective for achieving glycemic control for more than 2 years.

The reason for the reduction in postprandial glucose levels in the ‘vegetables before carbohydrate’ can be explained, partly, by the dietary fiber content in the vegetables taken before the carbohydrate.[11,12] The diet of the educational group that was rich in dietary fiber improved glucose tolerance by decreasing peak of postprandial glucose levels.[13] These results indicated that dietary carbohydrates consumed after vegetables were digested slowly and required less insulin for subsequent metabolic disposal. These changes would be expected to benefit subjects with diabetes, as they often delay secretion of insulin.[10] Numerous other factors may influence the glycemic response and digestion of carbohydrates in the small intestine. These include the rate of digestion,[14] type of food,[15] cooking method,[16] type of starch,[17] presence of α-amylase inhibitors,[17,18] transit time,[19] amount of protein and fat,[20] rate of gastric emptying,[21] rate of intestinal absorption,[22] hormonal gastrointestinal response,[23] hepatic glucose balance, and cellular metabolism of glucose. The patients in the educational group showed increased post-meal satiety and decreased subsequent hunger since they consumed a certain amounts of vegetables. This led them to decrease the intake of carbohydrate at the end of each meal. However, further studies are required to determine the details of the mechanisms responsible for these metabolic changes.

The aim of the study was to re-organize nutritional strategies for helping diabetic outpatients adhere to dietary regimens. We observed a significant reduction in HbA1c, blood pressure, body weight, and serum lipids levels in the educational group. The patients in the educational group had a significant increase in consumption of green vegetables and other vegetables, and a decreased consumption of grains and fruits compared to before the intervention. These findings are important, as they suggest the strategy of eating ‘vegetables before carbohydrate’ was successful in promoting patient’s education, particularly regarding consumption of food components. Although the strategy of education did not focus on restricting energy intake, the results showed patients reduced their intake of energy intake after intervention.

In our previous study, we also demonstrated the effect of this eating order method for the group education on the reduction of glycated hemoglobin, body weight, and serum lipids values in the participants with impaired glucose tolerance.[24] Additionally, participants showed improvements in their 2-hour postprandial blood glucose levels.

This approach of eating ‘vegetables before carbohydrate’ supports the concept of emphasizing food choices, what to eat first, how to eat and not just to concentrate on energy intake. With regard to nutritional approaches, our research showed nutritional advice should be given to patients with T2DM in the form of a simple and easy education, eating ‘vegetables before carbohydrate’.

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