



# Reducing Carbohydrate from Individual Sources Has Differential Effects on Glycosylated Hemoglobin in Type 2 Diabetes Mellitus Patients on Moderate Low-Carbohydrate Diets

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**Background:** We evaluated decreases in glycosylated hemoglobin (HbA1c) achieved by reducing carbohydrate from various sources in type 2 diabetes mellitus patients.

**Methods:** We followed up 138 male and 107 female outpatients on a moderate low-carbohydrate diet without diabetic medication for 6 months. Changes in carbohydrate sources ( $\Delta$ carbohydrate) were assessed from 3-day dietary records at baseline and 6 months, and associations with changes in HbA1c ( $\Delta$ HbA1c) were examined with Spearman's correlation coefficients ( $r_s$ ) and multiple regression analysis.

**Results:**  $\Delta$ HbA1c was  $-1.5\% \pm 1.6\%$  in men and  $-0.9\% \pm 1.3\%$  in women, while  $\Delta$ total carbohydrate was  $-115.3 \pm 103.7$  g/day in men and  $-63.6 \pm 71.1$  g/day in women. Positive associations with  $\Delta$ HbA1c were found for  $\Delta$ total carbohydrate ( $r_s=0.584$ ),  $\Delta$ carbohydrate from soft drinks (0.368), confectionery (0.361), rice (0.325), bread (0.221), Chinese soup noodles (0.199) in men, and  $\Delta$ total carbohydrate (0.547) and  $\Delta$ carbohydrate from rice (0.376) and confectionery (0.195) in women. Reducing carbohydrate sources by 50 g achieved decreases in HbA1c of 0.43% for total carbohydrate, 1.33% for soft drinks, 0.88% for confectionery, 0.63% for bread, 0.82% for Chinese soup noodles and 0.34% for rice in men and 0.45% for total carbohydrate, 0.67% for confectionery and 0.34% for rice in women, although mean reductions in carbohydrate from these sources were much smaller than that from rice.

**Conclusion:** Decreases in HbA1c achieved by reducing carbohydrate from soft drinks, confectionery, bread and Chinese soup noodles were 2- to 4-fold greater than that for rice. Our results will enable patients to decrease HbA1c efficiently (UMIN000009866).

**Keywords:** Bread; Candy; Carbonated beverages; Diabetes mellitus, type 2; Diet, carbohydrate-restricted; Dietary carbohydrates; Glycated hemoglobin A; Oryza

## INTRODUCTION

Meal tolerance tests have proven that blood glucose and serum insulin concentrations are largely dependent on carbohydrate intake [1,2]. In contrast, dietary protein and fat intakes have little effect on concentrations. Incremental rises in blood glucose after ingesting various carbohydrate sources differ greatly: 50 g

of carbohydrate from potatoes or rice raised blood glucose by 2/3 and 1/2, respectively, compared with the same amount of glucose [3]. Nevertheless, little quantitative information on the direct impact of carbohydrate sources on glycosylated hemoglobin (HbA1c) in patients with type 2 diabetes mellitus (T2DM) has been reported, except for fructose-containing sugars and fruits [4-6]. This is probably because it is ethically difficult to

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impose a diet consisting largely of carbohydrate-rich foods on patients for a few months. Meanwhile, a large number of interventional studies have revealed that low-carbohydrate diets had beneficial effects on glycemic control in patients with T2DM compared to low-fat diets [7,8]. Most studies, however, have paid attention to only total carbohydrate intake and ignored effects of carbohydrate sources on HbA1c.

In our previous study, we set goals in terms of effects of carbohydrate delta-reduction ( $\Delta$ carbohydrate g/day) on decreases in HbA1c levels ( $\Delta$ HbA1c) in patients with T2DM treated with a moderate carbohydrate diet [9]. It demonstrated that  $\Delta\%$ carbohydrate (energy percent of carbohydrate reduction) was not associated with  $\Delta$ HbA1c, and reducing total carbohydrate by 106 g decreased HbA1c by 1.0%. However, some patients who followed our moderate low-carbohydrate diet achieved a greater reduction in HbA1c levels than we expected. We speculated that this was because we did not take the effects of carbohydrate sources into account. Furthermore, our recent observational study in patients with T2DM not taking antidiabetic agents revealed that carbohydrate from soft drinks and noodles, whose amounts were less than that of rice, had a greater impact on HbA1c compared with carbohydrate from rice in men but not in women [10].

In the clinical setting, patients with T2DM need specific instructions on what carbohydrate sources they should preferentially reduce to achieve HbA1c targets efficiently. When patients reduce their intake of carbohydrate from various sources by 50 g equivalent to 1 bowl for rice, a 500 mL bottle for soft drinks, 2 slices for white bread, a large piece of cake for confectionery and 1 Chinese-style bowl for Chinese soup noodles, how much will HbA1c levels decrease due to each reduction? Also, will decreases in HbA1c levels due to reducing various carbohydrate sources differ from those achieved by reducing rice?

In consideration of the above, we designed this study to investigate and compare the effects of reducing various carbohydrate sources on decreases in HbA1c by sex in patients with T2DM treated with a 6-month moderate low-carbohydrate diet. We excluded patients taking any type of antidiabetic medication, which would lead to an incorrect estimate of changes in HbA1c.

## METHODS

### Patients

We recruited all new Japanese outpatients with T2DM and

HbA1c levels of 6.5% or above at Haimoto Clinic from March 2013 to June 2018. Both newly and previously diagnosed patients were enrolled. Exclusion criteria included: taking any type of oral hypoglycemic agent, insulin or steroid hormone from 3 months before baseline that would impact HbA1c levels; following strict carbohydrate restriction at baseline based on commercial diet therapies such as the Atkins diet; serum creatinine levels greater than 2.0 mg/dL (176.8  $\mu$ mol/L), ketoacidosis, soft drink ketosis, cancer, or decompensatory liver cirrhosis.

Of 159 eligible Japanese male outpatients, two declined to participate, nine were voluntarily lost to follow-up, one moved, four did not report dietary information, three suffered from cancer, and two took antidiabetic medications during the study period. Thus, 138 male patients were investigated. Of 117 eligible Japanese female outpatients, three declined to participate, five were voluntarily lost to follow-up, one suffered from cancer, and one took antidiabetic medications during the study period. Thus, 107 female patients were investigated.

After obtaining written informed consent, patients were followed up for 6 months. The main protocol for the present study was approved by the Ethical Committee of Aichi Syukutoku University and it was registered in University Hospital Medical Network (UMIN000009866) before its start.

### Moderate low-carbohydrate diet and glycemic control

The main principles of our moderate low-carbohydrate diet are as follows: first, to calculate carbohydrate intake from 3-day dietary records at baseline; second, to reduce carbohydrate intake according to patients' baseline carbohydrate intake and HbA1c levels [11,12]. Based on the results of our previous studies [9,13], patients were divided into three groups according to their baseline HbA1c:  $\leq 7.4\%$ , 7.5% to 8.9%, and  $\geq 9.0\%$ . Patients with HbA1c levels  $\leq 7.4\%$  were instructed to reduce carbohydrate by about 70 g, those with levels 7.5% to 8.9% were instructed to reduce carbohydrate by about 120 g and those with levels  $\geq 9.0\%$  to reduce carbohydrate by about 170 g. We instructed them to reduce major carbohydrate sources with reference to baseline 3-day dietary records. Patients were recommended to eat an amount of fat corresponding to the decrease in energy due to the reduced carbohydrate intake. A dietician (Shio Watanabe) gave instructions to all participants twice during the first month and once a month thereafter.

We provided dietary instruction tailored to each patient for maintaining optimal carbohydrate reduction. From the 2nd month, we asked patients to recall dietary details for 1 or 2 days

and, straightaway, roughly calculated daily total carbohydrate and carbohydrate from various sources every month. We asked patients with difficulty in remembering their dietary details to make 3-day written dietary records or take snapshots of all they had eaten for a few days. Based on the findings from interviewing patients every month, we adjusted total carbohydrate intake in units by 25 to 50 g/day. To achieve this, we determined several carbohydrate sources that should be reduced and presented patients with written instructions in this regard. In accordance with their individual likes and dislikes, patients selected carbohydrate sources for reduction by themselves. We relaxed carbohydrate restrictions if patients had over-reduced intakes or felt stress about the reductions. By this procedure, patients were able to achieve stable reductions in carbohydrate intake for the initial 3 months and maintain the reductions for the following 3 months as described previously [9,12,14].

The target HbA1c levels were based on the guidelines of the American Diabetes Association [15]. Patients were requested to maintain their usual level of physical activity throughout the study.

#### Sources of carbohydrate from various foods

Foods rich in carbohydrate content were divided into 13 groups (rice, noodles, bread, other wheat-based foods, potatoes, sugar and sweetenings, vegetables, fruits, dairy, confectionery, soft drinks, alcoholic drinks, and seasonings) according to the Japanese food composition table. "Noodles" were divided into four food groups: udon (thick white noodles), Chinese soup noodles and spaghetti made from wheat and soba made from buckwheat. "Other wheat-based foods" included gyoza (Chinese-style dumplings), shaomai (steamed dumplings), and okonomiyaki (Japanese-style pizza). "Potatoes" included sweet potatoes, taro, and yams. "Sugar and sweetenings" included non-artificial sweeteners for drinks tea and cooking. "Vegetables" included carbohydrate-rich ones, i.e., carrots, Indian lotus, pumpkin, tomatoes and burdock. "Fruits" were divided into five food groups, of which citrus fruits included mikan (mandarin oranges), oranges, and grapefruits. "Dairy" included milk, cheese, butter, and processed dairy foods such as ice cream. "Confectionery" included cakes, manjyu (buns with bean-jam filling), candy, chocolate, cookies, and snack foods (chips made from rice, wheat or potato with a sweet or salty taste). "Soft drinks" included beverages containing sugar, glucose, and fructose. "Alcoholic drinks" included brewed liquors: beer, sake (rice wine), chuhai (white distilled

liquor mixed with soda water and sweetenings), and wine, but did not include distilled liquors because they contain little carbohydrate.

#### Dietary records and clinical assessment

Intakes of total carbohydrate and carbohydrate sources were assessed at baseline and 6 months based on 3-day dietary records. Patients were requested to record dietary intakes on 3 non-consecutive days: 2 weekdays and a holiday. The dietary records were obtained within 2 weeks from the first visit to Haimoto Clinic and we measured the HbA1c level during this period. Patients were not instructed to make any dietary changes during that time. Supplementary information was obtained in an interview with a dietitian. Dietary intakes were computed from the dietary records using the Healthy Maker Pro 501 software (Mushroomsoft, Okayama, Japan).

We measured the body mass index (BMI) and HbA1c level of each patient every month. Venous blood samples were obtained after an overnight (12-hour) fast at baseline and 6 months for the determination of fasting plasma glucose, fasting serum insulin, triglycerides, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). The homeostasis model assessment of insulin resistance (HOMA-IR) parameter was computed as follows: [fasting plasma glucose (mg/dL)] × [fasting serum insulin (μIU/mL)]/405 [16].

Patients were asked about leisure-time physical activity levels in a questionnaire at baseline. The metabolic equivalents (Mets)-hour per week was calculated each week based on the intensity and duration of various leisure-time physical activities. We investigated changes in leisure-time physical activities during the study period in 83 patients (47 men, 36 women) who were registered after July 2016.

#### Laboratory methods

HbA1c levels were measured by high-performance liquid chromatography (Arkley Co., Kyoto, Japan) and presented as National Glycohemoglobin Standardization Program (NGSP) values (%). Plasma glucose concentrations were determined using enzymatic methods (Shino-Test Co., Kanagawa, Japan). Serum insulin levels were measured using the standard double antibody radioimmunoassay method (Fujirebio Inc., Tokyo, Japan). Enzymatic methods were used to measure serum triglyceride concentrations (Daiichi Pure Chemicals Co., Tokyo, Japan). Direct methods were used to assay serum LDL-C and HDL-C levels (Daiichi Pure Chemicals Co., Tokyo, Japan).

### Statistical analysis

The change in each biomarker ( $\Delta$ ) was defined as the level after 6 months minus the level at baseline. In the analysis, we included carbohydrate sources that were consumed by at least 30% of patients at baseline.

Increases in the selected baseline characteristics (age, BMI, HbA1c, leisure-time physical activities, total energy intake, and total carbohydrate intake) with increasing or decreasing trends in  $\Delta$ HbA1c were tested using linear regression models including an ordinal score for two to four groups. The Wilcoxon test was used to assess the changes in HbA1c levels and other cardiovascular risk factors, leisure-time physical activities, total energy, macronutrient intakes, and carbohydrate from various sources due to the moderate low-carbohydrate diet. We compared levels at baseline and after 6 months.

We computed Spearman's correlation coefficients ( $r_s$ ) to examine correlations of  $\Delta$ total carbohydrate (g/day) or  $\Delta$ carbohydrate (g/day) from sources with  $\Delta$ HbA1c. We considered the associations to be strong when  $r_s$  was  $\geq 0.5$ , moderate when  $r_s$  was  $\geq 0.3$  to  $< 0.5$  and weak when  $r_s$  was  $< 0.3$ .

Multiple regression analyses were performed to examine associations of  $\Delta$ total carbohydrate or  $\Delta$ carbohydrate from the sources (g/day) with  $\Delta$ HbA1c according to two models: adjustment for age and leisure time physical activities (Model 1), for

covariates in Model 1 plus  $\Delta$ BMI, for covariates in Model 1 plus  $\Delta$ BMI and  $\Delta$ total energy intake (Model 2). Regarding  $\Delta$ carbohydrate from non-staple foods, adjustment for  $\Delta$ carbohydrate from staple foods (rice, total noodles, and bread) was also conducted to eliminate the possible effects of  $\Delta$ carbohydrate due to them on  $\Delta$ HbA1c.

$P$  values less than 0.05 were considered statistically significant. Data are shown as mean  $\pm$  SD. All statistical analyses were performed using SPSS version 25.0 (IBM Co., Armonk, NY, USA).

## RESULTS

### HbA1c levels and clinical variables at baseline, changes in them during 6 months and changes in HbA1c according to selected baseline characteristics by sex

Tables 1 and 2 summarize clinical variables at baseline, their changes and changes in HbA1c according to the selected baseline characteristics in men ( $n=138$ ) and women ( $n=107$ ). Compared to baseline, the mean HbA1c levels significantly decreased over 6 months in both sexes, by  $1.5\% \pm 1.6\%$  ( $15.6 \pm 16.1$  mmol/mol) from  $8.3\% \pm 1.7\%$  ( $64.2 \pm 17.0$  mmol/mol) at baseline in men, and by  $0.9\% \pm 1.3\%$  ( $9.5 \pm 13.0$  mmol/mol) from  $7.8\% \pm 1.5\%$  ( $59.6 \pm 7.0$  mmol/mol) at baseline in women

**Table 1.** HbA1c levels and cardiovascular risk factors at baseline and their changes during 6 months by sex

Variable	Men ( $n=138$ )			Women ( $n=107$ )		
	Baseline	Changes	$P$ value	Baseline	Changes	$P$ value
Age	60.0 $\pm$ 11.0			61.8 $\pm$ 10.4		
Duration of diabetes, mo	26.9 $\pm$ 52.8			23.2 $\pm$ 51.3		
Leisure-time physical activities (Mets), hr/wk	6.1 $\pm$ 10.9			5.3 $\pm$ 10.0		
BMI, kg/m <sup>2</sup>	25.5 $\pm$ 3.5	-0.8 $\pm$ 1.2	<0.001	25.1 $\pm$ 4.1	-0.8 $\pm$ 1.3	<0.001
HbA1c, %	8.3 $\pm$ 1.7	-1.5 $\pm$ 1.6	<0.001	7.8 $\pm$ 1.5	-0.9 $\pm$ 1.3	<0.001
HbA1c, mmol/mol	64.2 $\pm$ 17.0	-15.6 $\pm$ 16.1	<0.001	59.6 $\pm$ 7.0	-9.5 $\pm$ 13.0	<0.001
Plasma glucose levels, mmol/L	8.16 $\pm$ 2.05	-1.17 $\pm$ 1.72	<0.001	7.66 $\pm$ 2.44	-0.94 $\pm$ 1.72	<0.001
Fasting insulin levels, pmol/L	52.4 $\pm$ 32.4	-6.74 $\pm$ 23.5	<0.001	58.4 $\pm$ 42.3	-5.1 $\pm$ 29.0	0.014
HOMA-IR	2.69 $\pm$ 1.69	-0.61 $\pm$ 1.41	<0.001	2.81 $\pm$ 2.01	-0.46 $\pm$ 1.56	<0.001
LDL-C, mmol/L <sup>a</sup>	3.42 $\pm$ 0.91	-0.18 $\pm$ 0.96	0.043	3.52 $\pm$ 0.78	-0.10 $\pm$ 0.83	0.239
HDL-C, mmol/L <sup>a</sup>	1.30 $\pm$ 0.28	0.13 $\pm$ 0.23	<0.001	1.50 $\pm$ 0.36	0.13 $\pm$ 0.23	<0.001
Triglycerides, mmol/L <sup>a</sup>	1.83 $\pm$ 2.44	-0.44 $\pm$ 1.89	<0.001	1.53 $\pm$ 1.07	-0.28 $\pm$ 0.69	0.003

Values are presented as mean  $\pm$  standard deviation.

HbA1c, glycosylated hemoglobin; Mets, metabolic equivalents; BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

<sup>a</sup>Patients who took lipid-lowering medications (30 for men and 38 for women) were excluded for analysis.

**Table 2.** Changes in HbA1c levels during 6 months according to selected baseline characteristics by sex

Baseline characteristic	Men (n=138)			Women (n=107)		
	Number	Changes in HbA1c, %	P for trend	Number	Changes in HbA1c, %	P for trend
Age, yr						
<65	89	-1.8±0.2		57	-1.1±0.2	
≥65	49	-1.1±0.2	0.025	50	-0.7±0.1	0.126
BMI, kg/m <sup>2</sup>						
<20.0	7	-1.2±0.8		9	-0.4±0.3	
20.0–24.9	57	-1.4±0.2		45	-0.7±0.1	
24.9–29.9	62	-1.7±0.2		39	-1.2±0.3	
≥30.0	12	-1.7±0.3	0.318	14	-1.1±0.2	0.050
HbA1c						
6.5%–7.4%	63	-0.4±0.1		63	-0.3±0.1	
7.5%–8.9%	36	-1.3±0.1		26	-1.1±0.1	
≥9.0%	39	-3.5±2.3	<0.001	18	-3.1±0.4	<0.001
Leisure-time physical activities (Mets), hr/wk						
0	84	-1.6±0.2		58	-0.9±0.2	
1.0–10.9	28	-1.8±0.3		30	-1.0±0.3	
≥11.0	26	-1.1±0.2	0.376	19	-0.8±0.2	0.919
Total energy intake						
1st tertile <sup>a</sup>	46	-1.1±0.2		36	-0.6±0.2	
2nd tertile <sup>a</sup>	46	-1.2±0.2		36	-0.5±0.1	
3rd tertile <sup>a</sup>	46	-2.3±0.3	<0.001	35	-1.7±0.3	<0.001
Total carbohydrate intake						
1st tertile <sup>b</sup>	46	-0.8±0.1		36	-0.6±0.1	
2nd tertile <sup>b</sup>	46	-1.3±0.2		36	-0.8±0.2	
3rd tertile <sup>b</sup>	46	-2.4±0.3	<0.001	35	-1.5±0.3	0.003

Values are presented as mean ± standard deviation.

HbA1c, glycosylated hemoglobin; BMI, body mass index; Mets, metabolic equivalents.

<sup>a</sup>1st tertile (1,029–1,944 kcal for men, 881–1,539 kcal for women), 2nd tertile (1,945–2,405 kcal for men, 1,540–1,858 kcal for women), 3rd tertile (2,406–6,284 kcal for men, 1,859–3,408 kcal for women), <sup>b</sup>1st tertile (134.0–240.5 g/day for men, 108.7–196.8 g/day for women), 2nd tertile (240.6–308.9 g/day for men, 196.9–251.1 g/day for women), 3rd tertile (309.0–676.7 g/day for men, 251.2–512.6 g/day for women).

(Table 1). The higher HbA1c, total energy intake and total carbohydrate intake at baseline, the greater were reductions in HbA1c in both sexes (Table 2). Men aged less than 65 years had greater decreases in HbA1c compared with older men.

We investigated changes in leisure-time physical activities in 83 patients (47 male and 36 female) who were registered after July 2016. The 47 male patients had significantly higher mean leisure-time physical activities (8.4±13.5 Mets hr/wk) than the other male patients (n=91, 4.8±1.0 Mets hr/wk) at baseline and significantly increased them during the 6 months (11.2±16.9 Mets hr/wk; P=0.017), whereas the 36 female patients had leisure-time physical activities of 4.4±0.9 Mets hr/wk at base-

line that were not significantly different (P=0.126) compared with the other female patients (n=71, 5.7±1.3 Mets hr/wk) and did not change them (4.4±0.8 Mets hr/wk; P=0.490).

The mean BMI, plasma glucose levels, fasting insulin levels, HOMA-IR, serum HDL-C and triglyceride levels significantly improved in both sexes, and LDL-C levels significantly decreased in men but not women (Table 1).

#### Total carbohydrate, carbohydrate from sources and their changes during 6 months by sex

Tables 3 (men) and 4 (women) show macronutrients, total carbohydrate and carbohydrate from sources at baseline and after 6



**Table 3.** Carbohydrate, its sources and changes in them from baseline to 6 months in men ( $n=138$ )

Macronutrients	Baseline	% <sup>a</sup>	6 months	% <sup>a</sup>	Changes	P value
Total energy, kcal	2,285±753		1,846±521		-439±660	<0.001
Total carbohydrate, g	285.0±93.7		170.0±57.8		-115.3±103.7	<0.001
Carbohydrate, % energy	50.8±9.7		37.8±11.5		-13.0±11.3	<0.001
Protein, g	80.0±23.9		81.5±27.5		1.5±26.0	0.797
Protein, % energy	14.2±2.4		17.7±3.3		3.5±3.7	<0.001
Fat, g	69.9±30.0		75.6±32.3		5.8±32.5	<0.001
Fat, % energy	27.3±7.0		36.5±9.6		9.2±10.4	<0.001
Carbohydrate sources, g						
Rice	117.8±55.9	100	61.0±41.7	94	-56.9±58.9	<0.001
Total noodles	35.8±33.4	85	20.2±21.2	70	-15.6±36.6	<0.001
Udon	8.8±17.2	35	5.6±10.7	27	-3.2±17.4	0.056
Chinese soup noodles	19.0±26.1	58	10.4±16.4	41	-8.6±29.6	0.001
Soba <sup>b</sup>	3.4±8.5	17	2.6±7.9	12	-0.7±10.9	
Spaghetti <sup>b</sup>	4.6±11.6	27	1.5±4.8	15	-3.1±12.4	
Bread	24.3±22.9	84	18.8±18.4	76	-5.4±21.6	0.002
Other wheat-based foods	8.3±7.1	90	7.4±7.3	84	-0.8±9.6	0.187
Potatoes	8.3±7.1	94	5.3±5.1	91	-1.6±8.8	0.066
Sugar and sweetenings	6.2±6.1	99	4.6±4.3	95	-1.6±6.1	0.013
Vegetables	8.0±6.0	100	8.1±5.2	100	0.1±7.4	0.718
Total fruits	11.4±17.4	65	7.0±13.2	53	-4.4±19.5	0.009
Bananas <sup>b</sup>	4.2±8.7	26	1.7±5.8	14	-2.5±9.1	
Citrus fruits	2.1±6.0	34	0.8±2.3	23	-1.3±6.4	0.008
Apples <sup>b</sup>	2.2±10.6	18	1.7±4.6	18	-0.5±11.4	
Fruits juice <sup>b</sup>	1.6±5.4	20	0.4±2.4	22	-1.2±5.7	
Dairy	5.7±8.2	80	3.6±5.2	80	-2.0±7.9	0.005
Confectionery	15.5±24.7	64	6.1±11.1	56	-9.4±23.1	<0.001
Soft drinks	13.0±26.2	83	2.8±4.8	75	-10.2±26.7	<0.001
Total alcoholic drinks	7.7±15.8	74	1.4±4.7	64	-6.3±15.9	<0.001
Beer	6.6±14.8	34	1.1±4.6	15	-5.5±14.9	<0.001
Sake	0.7±3.3	65	0.2±0.7	56	-0.5±3.1	0.015
Chuhai <sup>b</sup>	0.4±2.3	4	0.04±0.28	2	-0.4±3.2	
Wine <sup>b</sup>	0.02±0.13	6	0.02±0.17	5	0.0±0.2	
Seasonings	10.8±4.8	100	9.2±4.3	100	-1.7±5.7	0.001
Dietary fiber	0.7±0.5	93	0.6±0.5	89	-0.1±0.6	0.084

Values are presented as mean ± standard deviation.

<sup>a</sup>Percent of patients who consumed the carbohydrate sources, <sup>b</sup>In the analysis, we excluded carbohydrate sources that were consumed by less than 30% of patients at baseline.

months and their changes. The average total carbohydrate (g/day) significantly decreased in both sexes, from 285.0±93.7 to 170.0±57.8 g (-115.3±103.7 g) in men and from 229.9±67.3 to 166.3±

42.6 g (-63.6±71.1 g) in women. Tables 3 and 4 also show percentages of patients who consumed each carbohydrate source (%). Since the percentage of patients who consumed the follow-

**Table 4.** Carbohydrate intake, its sources and changes in them from baseline to 6 months in women (*n* = 107)

Macronutrients	Baseline	% <sup>a</sup>	6 months	% <sup>a</sup>	Changes	<i>P</i> value
Total energy, kcal	1,745±431		1,553±342		-192±438	<0.001
Total carbohydrate, g	229.9±67.3		166.3±42.6		-63.6±71.1	<0.001
Carbohydrate, % energy	52.6±7.7		43.5±9.3		-9.1±9.7	<0.001
Protein, g	67.6±14.8		70.4±18.0		2.8±19.4	0.180
Protein, % energy	15.8±2.5		18.2±2.9		2.4±3.3	<0.001
Fat, g	58.0±21.1		63.7±23.3		5.7±22.8	0.022
Fat, % energy	29.8±6.9		36.2±8.0		6.5±8.5	<0.001
Carbohydrate sources, g						
Rice	85.7±45.0	100	53.3±31.3	100	-32.4±41.7	<0.001
Total noodles	18.4±15.9	78	16.2±16.7	68	-2.2±20.7	0.288
Udon	5.7±8.8	35	5.7±10.4	29	0.1±13.1	0.948
Chinese soup noodles	7.3±12.6	32	5.3±9.1	30	-2.0±16.2	0.269
Soba <sup>b</sup>	1.8±5.1	12	2.5±6.8	17	0.8±7.6	
Spaghetti <sup>b</sup>	3.7±8.5	25	2.6±6.5	20	-1.0±10.4	
Bread	25.0±19.5	84	21.2±17.6	85	-3.8±22.0	0.028
Other wheat-based foods	8.5±9.2	92	7.7±7.9	92	-0.8±11.3	0.692
Potatoes	5.4±5.3	89	4.0±4.5	89	-1.4±6.9	0.023
Sugar and sweetenings	8.9±9.3	96	6.1±5.8	95	-2.8±10.2	0.004
Vegetables	9.6±6.0	100	8.6±5.0	100	-0.9±6.7	0.307
Total fruits	13.1±15.7	81	10.0±11.8	73	-3.5±15.5	0.040
Bananas <sup>b</sup>	2.6±6.6	23	1.2±3.5	13	-1.4±6.9	
Citrus fruits	2.5±5.0	43	1.8±5.1	38	-0.8±7.4	0.061
Apples	2.8±4.8	31	2.5±5.0	32	-0.3±5.9	0.372
Fruits juice <sup>b</sup>	0.6±2.2	27	0.2±1.2	15	-0.4±2.4	
Dairy	5.4±6.1	87	3.6±4.4	82	-1.7±6.1	0.002
Confectionery	19.8±23.9	85	9.2±11.7	68	-10.6±24.0	<0.001
Soft drinks	7.7±25.0	86	2.3±3.4	85	-5.3±24.8	0.292
Total alcoholic drinks	0.9±2.9	62	0.4±1.5	63	-0.4±3.2	0.595
Beer <sup>b</sup>	0.4±2.1	6	0.3±1.3	5	-0.1±2.5	
Sake	0.2±0.9	51	0.1±0.1	52	-0.1±0.8	0.529
Chuhai <sup>b</sup>	0.2±1.8	3	0.03±0.26	1	-0.22±1.72	
Wine <sup>b</sup>	0.03±0.27	6	0.01±0.08	6	-0.02±0.28	
Seasonings	8.9±3.8	100	9.4±3.8	100	0.5±4.8	0.299
Dietary fiber	0.7±0.5	92	0.7±0.5	93	0.1±0.6	0.142

Values are presented as mean ± standard deviation.

<sup>a</sup>Percent of patients who consumed the carbohydrate sources, <sup>b</sup>In the analysis, we excluded carbohydrate sources that were consumed by less than 30% of patients at baseline.

ing carbohydrate sources was <30% at baseline, we eliminated them from the analysis: soba, spaghetti, bananas, apples, fruits juice, chuhai and wine in men; soba, spaghetti, bananas, fruits

juice, beer, chuhai, and wine in women.

Intake from 14 carbohydrate sources significantly decreased over 6 months in men (rice, total noodles, Chinese soup noo-

**Table 5.** Association of changes in intake of carbohydrate and its sources with changes in glycosylated hemoglobin (%) in men ( $n=138$ )

Carbohydrate and its sources	Spearman's coefficients		Regression model								
	$r_s$	$P$ value	Crude			Model 1			Model 2		
			$\beta$	SE	$P$ value	$\beta$	SE	$P$ value	$\beta$	SE	$P$ value
$\Delta$ Total carbohydrate	0.584	<0.001	0.456	0.052	<0.001	0.426	0.055	<0.001	0.451	0.085	<0.001
$\Delta$ Carbohydrate from sources											
$\Delta$ Rice	0.325	<0.001	0.420	0.109	<0.001	0.335	0.110	0.003	0.052	0.123	0.671
$\Delta$ Total noodles	0.157	0.065	0.558	0.178	0.002	0.428	0.180	0.019	0.250	0.171	0.146
$\Delta$ Udon	-0.140	0.102	-0.649	0.385	0.094	-0.651	0.368	0.080	-0.547	0.337	0.107
$\Delta$ Chinese soup noodles	0.199	0.019	0.998	0.212	<0.001	0.822	0.219	<0.001	0.608	0.215	0.005
$\Delta$ Bread	0.221	0.009	0.696	0.307	0.025	0.633	0.295	0.034	0.331	0.279	0.238
$\Delta$ Other wheat-based foods	0.043	0.613	0.131	0.702	0.852	0.166	0.672	0.805	-0.796	0.642	0.217
$\Delta$ Potatoes	-0.025	0.773	-0.460	0.771	0.552	-0.511	0.744	0.452	-0.514	0.690	0.458
$\Delta$ Sugar and sweetenings	0.056	0.515	0.484	1.101	0.661	0.707	1.057	0.504	-0.588	0.999	0.557
$\Delta$ Vegetables	0.004	0.997	0.047	0.904	0.958	0.052	0.866	0.952	-0.071	0.796	0.929
$\Delta$ Total fruits	0.134	0.118	0.932	0.338	0.007	0.923	0.329	0.006	0.789	0.303	0.010
$\Delta$ Citrus fruits	0.001	0.988	0.999	1.054	0.345	1.329	1.027	0.198	1.240	0.937	0.188
$\Delta$ Dairy	0.151	0.077	2.450	0.831	0.004	2.435	0.795	0.003	2.077	0.772	0.008
$\Delta$ Confectionery	0.361	<0.001	0.830	0.284	0.004	0.879	0.270	0.001	0.580	0.259	0.027
$\Delta$ Soft drinks	0.368	<0.001	1.439	0.221	<0.001	1.326	0.220	<0.001	1.110	0.214	<0.001
$\Delta$ Total alcoholic drinks	0.128	0.135	1.146	0.411	0.006	0.780	0.416	0.063	0.085	0.411	0.836
$\Delta$ Beer	0.134	0.118	1.234	4.390	0.006	0.865	0.442	0.052	0.338	0.424	0.426
$\Delta$ Sake	0.008	0.924	0.739	2.138	0.730	0.600	2.049	0.770	-2.035	1.923	0.292
$\Delta$ Seasonings	0.124	0.149	1.756	1.170	0.136	1.211	1.140	0.290	-1.235	1.132	0.277
$\Delta$ Dietary fiber	-0.016	0.848	2.773	11.418	0.809	0.022	11.167	0.998	-8.846	10.685	0.408

Regression coefficients and their SEs are indicated per 50 g carbohydrate. The change in glycosylated hemoglobin and carbohydrate sources ( $\Delta$ ) was defined as the level after 6 months minus the level at baseline. Model 1: adjusted for age and physical activities. Model 2: adjusted for covariates in Model 1 plus  $\Delta$ body mass index and  $\Delta$ total energy intake.

SE, standard error.

dles, bread, sugar and sweetenings, total fruits, citrus fruits, dairy, confectionery, soft drinks, total alcoholic drinks, beer, sake, and seasonings) (Table 3).  $\Delta$ carbohydrate from rice was greatest and accounted for about 50% of  $\Delta$ total carbohydrate, followed by that from soft drinks, confectionery, Chinese soup noodles, beer and bread, and means of  $\Delta$ carbohydrate from these sources were much smaller, 1/5 to 1/10 of that from rice.

Intake from seven carbohydrate sources significantly decreased in women (rice, bread, potatoes, sugar and sweetenings, total fruits, dairy, and confectionery) (Table 4).  $\Delta$ carbohydrate from rice accounted for about 50% of  $\Delta$ total carbohydrate, followed by that from confectionery, soft drinks, bread and total fruits, and means of  $\Delta$ carbohydrate from these sources

were small, 1/3 to 1/10 of that from rice.

#### Associations of $\Delta$ total carbohydrate and $\Delta$ carbohydrate from sources with $\Delta$ HbA1c in men

In men, Spearman correlation coefficients indicated positive correlations with  $\Delta$ HbA1c for  $\Delta$ total carbohydrate and  $\Delta$ carbohydrate from five sources (Table 5 and Supplementary Fig. 1A-F). The coefficient was greatest for  $\Delta$ total carbohydrate ( $r_s=0.584$ ), followed by  $\Delta$ carbohydrate from soft drinks ( $r_s=0.368$ ), confectionery ( $r_s=0.361$ ), rice ( $r_s=0.325$ ), bread ( $r_s=0.221$ ), and Chinese soup noodles ( $r_s=0.199$ ) in descending order. There was a strong association for  $\Delta$ total carbohydrate and associations were moderate for  $\Delta$ carbohydrate from soft drinks,



confectionery and rice and weak for  $\Delta$ carbohydrate from bread and Chinese soup noodles.

According to multiple regression analyses with adjustment for age and leisure-time physical activity (Model 1), reducing total carbohydrate by 50 g was associated with a decrease in HbA1c of 0.43% and reducing carbohydrate from soft drinks, confectionery, rice, bread, and Chinese soup noodles by 50 g was correlated with decreases of 1.33%, 0.88%, 0.34%, 0.63%, and 0.82%, respectively (Table 5). With adjustment for the covariates in Model 1 plus  $\Delta$ BMI, the results were almost the same:  $\Delta$ total carbohydrate,  $\beta=0.419$ ,  $SE=0.055$ ,  $P<0.001$ ;  $\Delta$ carbohydrate from soft drinks,  $\beta=1.313$ ,  $SE=0.208$ ,  $P<0.001$ ; that from confectionery,  $\beta=0.854$ ,  $SE=0.248$ ,  $P=0.002$ ; that

from rice,  $\beta=0.312$ ,  $SE=0.110$ ,  $P=0.005$ ; that from bread,  $\beta=0.604$ ,  $SE=0.292$ ,  $P=0.041$ ; that from Chinese soup noodles,  $\beta=0.873$ ,  $SE=0.216$ ,  $P<0.001$ . Changes in  $\beta$  compared with the basic Model 1 ranged from 0.007% to 0.051%.

With the adjustments in Model 2 (covariates in Model 1 plus  $\Delta$ BMI and  $\Delta$ total energy intake), the positive correlations for  $\Delta$ carbohydrate from rice and bread were no longer significant, but correlations remained significant for  $\Delta$ total carbohydrate and  $\Delta$ carbohydrate from soft drinks, confectionery and Chinese soup noodles (Table 5).

Regarding soft drinks and confectionery, we conducted the analysis with adjustment for  $\Delta$ carbohydrate from the staple foods (rice, total noodles, and bread). The positive correlations

**Table 6.** Association of changes in intake of carbohydrate and its sources with changes in glycosylated hemoglobin (%) in women ( $n=107$ )

Carbohydrate and its sources	Spearman's coefficients		Regression model								
	$r_s$	P value	Crude			Model 1			Model 2		
			$\beta$	SE	P value	$\beta$	SE	P value	$\beta$	SE	P value
$\Delta$ Total carbohydrate	0.547	<0.001	0.470	0.075	<0.001	0.447	0.075	<0.001	0.494	0.124	<0.001
$\Delta$ Carbohydrate from sources											
$\Delta$ Rice	0.376	<0.001	0.392	0.144	0.008	0.340	0.144	0.020	0.166	0.145	0.255
$\Delta$ Total noodles	0.163	0.093	0.473	0.298	0.115	0.497	0.292	0.092	0.060	0.289	0.835
$\Delta$ Udon	0.087	0.370	0.423	0.474	0.374	0.511	0.465	0.274	0.019	0.446	0.966
$\Delta$ Chinese soup noodles	0.038	0.695	-0.006	0.384	0.988	-0.179	0.383	0.640	-0.224	0.351	0.525
$\Delta$ Bread	0.102	0.295	0.290	0.282	0.306	0.325	0.277	0.245	0.247	0.255	0.336
$\Delta$ Other wheat-based foods	-0.017	0.864	1.263	0.538	0.021	1.326	0.525	0.013	0.968	0.499	0.055
$\Delta$ Potatoes	-0.019	0.846	0.036	0.898	0.968	0.056	0.871	0.950	-0.687	0.823	0.406
$\Delta$ Sugar and sweetenings	0.163	0.093	2.277	0.570	<0.001	2.120	0.567	<0.001	1.710	0.536	0.002
$\Delta$ Vegetables	0.156	0.110	1.582	0.923	0.089	1.302	0.921	0.160	-0.087	0.907	0.923
$\Delta$ Total fruits	0.127	0.193	0.102	0.402	0.801	0.133	0.394	0.736	-0.317	0.378	0.404
$\Delta$ Citrus fruits	-0.129	0.186	-1.306	0.836	0.121	-1.397	0.818	0.091	-0.800	0.773	0.303
$\Delta$ Apples	-0.055	0.574	-0.213	1.059	0.841	-0.039	1.034	0.970	-0.421	0.970	0.665
$\Delta$ Dairy	0.161	0.098	1.624	1.013	0.112	1.489	1.001	0.140	0.743	0.937	0.430
$\Delta$ Confectionery	0.195	0.044	0.616	0.253	0.016	0.670	0.247	0.008	0.219	0.261	0.404
$\Delta$ Soft drinks	0.106	0.276	0.644	0.243	0.009	0.532	0.247	0.033	0.364	0.240	0.134
$\Delta$ Total alcoholic drinks	0.132	0.174	5.430	1.851	0.004	5.317	1.814	0.004	3.969	1.713	0.023
$\Delta$ Sake	0.054	0.580	-1.230	7.340	0.867	-1.515	7.215	0.834	1.270	6.794	0.852
$\Delta$ Seasonings	0.019	0.848	0.946	1.297	0.467	1.275	1.275	0.319	-0.439	1.257	0.728
$\Delta$ Dietary fiber	0.133	0.172	16.164	10.173	0.115	16.030	9.977	0.111	9.556	9.302	0.307

Regression coefficients and their SEs are indicated per 50 g carbohydrate. The change in glycosylated hemoglobin and carbohydrate sources ( $\Delta$ ) was defined as the level after 6 months minus the level at baseline. Model 1: adjusted for age and physical activities. Model 2: adjusted for covariates in Model 1 plus  $\Delta$ body mass index and  $\Delta$ total energy intake. SE, standard error.

of  $\Delta$ carbohydrate from soft drinks ( $\beta=1.286$ ,  $SE=0.202$ ,  $P<0.001$ ) and confectionery ( $\beta=0.542$ ,  $SE=0.270$ ,  $P=0.047$ ) remained significant.

#### Association of $\Delta$ total carbohydrate and $\Delta$ carbohydrate from sources with $\Delta$ HbA1c in women

In women,  $\Delta$ total carbohydrate and  $\Delta$ carbohydrate from two sources had positive associations with  $\Delta$ HbA1c (Table 6 and Supplementary Fig. 1G-I) according to Spearman's correlation coefficients. The coefficient was greatest for  $\Delta$ total carbohydrate ( $r_s=0.547$ ) followed by  $\Delta$ carbohydrate from rice ( $r_s=0.376$ ), and confectionery ( $r_s=0.195$ ) in descending order. Thus, there was a strong association for  $\Delta$ total carbohydrate, a moderate association for  $\Delta$ carbohydrate from rice and a weak association for  $\Delta$ carbohydrate from confectionery.

Multiple regression analyses with adjustment for age and leisure-time physical activities (Model 1) revealed that reducing total carbohydrate by 50 g was associated with a decrease in HbA1c of 0.45% and that reducing carbohydrate from rice and confectionery by 50 g was associated with a decrease in HbA1c of 0.34% and 0.67%, respectively (Table 6). With adjustment for the covariates in Model 1 plus  $\Delta$ BMI, the significance for carbohydrate sources did not change, but the regression coefficient for  $\Delta$ carbohydrate from confectionery slightly decreased:  $\Delta$ total carbohydrate,  $\beta=0.416$ ,  $SE=0.075$ ,  $P<0.001$ ;  $\Delta$ carbohydrate from rice,  $\beta=0.322$ ,  $SE=0.140$ ,  $P=0.023$ ; that from confectionery,  $\beta=0.528$ ,  $SE=0.250$ ,  $P=0.037$ . Changes in  $\beta$  compared with the basic Model 1 ranged from 0.018% to 0.142%.

With adjustment for the covariates in Model 1 plus  $\Delta$ BMI and  $\Delta$ total energy intake (Model 2), the positive correlations were no longer significant for  $\Delta$ carbohydrate from rice and confectionery, but remained significant for  $\Delta$ total carbohydrate (Table 6).

With adjustment for  $\Delta$ carbohydrate from the staple foods, the significant positive correlation disappeared for  $\Delta$ carbohydrate from confectionery ( $\beta=0.427$ ,  $SE=0.250$ ,  $P=0.09$ ).

## DISCUSSION

The current study showed that: (1) the mean reductions in HbA1c were 1.5% in men and 0.9% in women, while those in total carbohydrate were 115.3 g/day in men and 63.6 g/day in women; (2)  $\Delta$ total carbohydrate was positively and strongly correlated with  $\Delta$ HbA1c in both sexes and reducing total car-

bohydrate by 50 g was associated with a decrease in HbA1c of 0.43% in men and 0.45% in women; (3) there were positive, moderate or weak correlations of  $\Delta$ carbohydrate from soft drinks, confectionery, rice, bread, and Chinese soup noodles with  $\Delta$ HbA1c in men and reducing carbohydrate from these sources by 50 g was associated with decreases in HbA1c of 1.33%, 0.88%, 0.34%, 0.63%, and 0.82%, respectively; (4) there were positive, moderate, or weak correlations of  $\Delta$ carbohydrate from rice and confectionery with  $\Delta$ HbA1c and reducing carbohydrate from rice and confectionery by 50 g was associated with a decrease in HbA1c of 0.34% and 0.67%, respectively, in women; (5) the mean reductions in carbohydrate from soft drinks, confectionery, bread, and Chinese soup noodles were very small, 1/5 to 1/10 of that from rice in men and that from confectionery was also small in women, 1/3 of that from rice.

There are two confounding factors to be considered from a clinical point of view. First, with respect to  $\Delta$ BMI, the significance for carbohydrate sources did not change as compared with the basic Model 1 when adjustment was carried out with  $\Delta$ BMI added to the covariates in both sexes, although the regression coefficient for  $\Delta$ carbohydrate from confectionery slightly decreased in women. As the effects of carbohydrate reductions on decreases in HbA1c are partly mediated by weight loss,  $\Delta$ BMI is statistically regarded as an intermediate variable. We therefore considered regression coefficients from the basic Model 1 without  $\Delta$ BMI as clinically relevant. Second, the significance of  $\Delta$ carbohydrate from rice disappeared with the additional adjustment for  $\Delta$ total energy intake in Model 2, which may be relevant to the reduction in total energy intake of 10% to 20% during the study period. The reduction in total energy was due to reduction in carbohydrate intakes because only these intakes decreased; mean protein and fat intakes increased during the study period in both sexes. Rice is the major carbohydrate source in Japan and the reduction in carbohydrate from rice accounted for up to 50% of reduction in total carbohydrate in the current study. Our purpose is to obtain clinically useful information for dietary instruction given to patients in East and South Asia including Japan where the major carbohydrate source is rice. We want to know decreases in HbA1c per unit reduction in various carbohydrate sources even if the decrease is partially due to the reduction in energy intake. In this regard, adjustment for  $\Delta$ total energy intake would lead to underestimation of the regression coefficients for associations of  $\Delta$ HbA1c with  $\Delta$ carbohydrate from staple foods, especially rice. We, therefore, considered the regression coefficient from the

basic Model 1 (without  $\Delta$ BMI and  $\Delta$ total energy intake) as a clinically relevant measure.

Patients consume many types of carbohydrate sources, usually three staple ones, i.e., rice, noodles and bread, that account for 60% of total carbohydrate, together with non-staple carbohydrate sources. In this regard,  $\Delta$ carbohydrate from soft drinks and confectionery still remained significant after adjustment for  $\Delta$ carbohydrate from the three staple foods in men. This suggests that the effects of reducing carbohydrate from the above non-staple carbohydrate sources are independent of carbohydrate from the three staple foods.

In spite of the small reductions, the regression coefficient of the regression lines for these carbohydrate sources was highest for  $\Delta$ carbohydrate from soft drinks, followed by that from confectionery, Chinese soup noodles, bread, and rice in descending order in men. The effects of  $\Delta$ carbohydrate from the sources on  $\Delta$ HbA1c were 4-fold greater for soft drinks and 2.5-fold greater for confectionery, respectively, compared with rice. This is a reason why some patients who followed our previous moderate low-carbohydrate diet that ignored carbohydrate sources achieved a greater reduction in HbA1c levels than we expected [9]. We frequently experience rapid deterioration in HbA1c levels with excess consumption of soft drinks [17], and our results clearly explain the reason for this. Large-scale long-term cohort studies have indicated increases in mortality from cancer or cardiovascular diseases in people with strict carbohydrate restrictions [18-20] and therefore, patients need a diet with less strict carbohydrate restriction, namely a moderate low-carbohydrate diet. Notably, 41% of the male patients and 59% female patients were consuming amounts (i.e., over 40% of total carbohydrate intake) of carbohydrate from non-staple foods, such as soft drinks and confectionery, at baseline that could not be ignored. In the clinical setting, patients should preferentially reduce carbohydrate from soft drinks or confectionery over that from rice and our results may enable them to achieve effective decreases in HbA1c by reducing carbohydrate from its sources by small amounts.

Although values of  $\Delta$ carbohydrate from bread and Chinese soup noodles were small, 1/7 to 1/10 of that from rice, and their associations with  $\Delta$ HbA1c were weak, reducing carbohydrate from bread and Chinese soup noodles by 50 g was associated with decreases in HbA1c of 0.63% and 0.82%, respectively, in men, which were 2- and 2.5-fold greater than that from rice, respectively. As a possible explanation, single servings of Chinese soup noodles (7 g salt) and bread (2 g salt) have a higher

sodium chloride concentration than rice (0 g salt). Glucose absorption taking place in small intestinal cells is mediated by the sodium-glucose co-transporter 1 (SGLT1), which is driven by sodium extrusion [21]. Also, animal experiments have demonstrated that dietary sodium chloride increases intestinal glucose absorption by increasing the expression of SGLT1 in the intestine [22]. Although there is no clinical data on the effects of dietary sodium chloride on blood glucose, it is theoretically possible that foods containing more sodium chloride may have a stronger hyperglycemic effect. Therefore, in this regard, further studies on the effects of carbohydrate sources containing a large amount of salt on HbA1c are needed.

The question is: why were the associations of  $\Delta$ carbohydrate from soft drinks and confectionery with  $\Delta$ HbA1c stronger than for  $\Delta$ carbohydrate from rice in men, although the means of  $\Delta$ carbohydrate from soft drinks and confectionery were very small, about one fifth of  $\Delta$ carbohydrate from rice? From a statistical point of view, despite the lower means of  $\Delta$ carbohydrate from soft drinks and confectionery, there was greater inter-individual variation while the reverse was so for  $\Delta$ carbohydrate from rice. This could possibly have led to the stronger correlations. Specifically, there was no carbohydrate intake from soft drinks or only a small amount of intake (<5.0 g/day) in 73% of men, who had lower HbA1c levels at baseline, and later exhibited only a small reduction in carbohydrate from soft drinks with little change in HbA1c. In contrast, the remaining 27% had a greater carbohydrate intake from soft drinks and higher HbA1c levels at baseline, and they had a greater reduction in carbohydrate from soft drinks and greater decreases in HbA1c levels. From a clinical point of view, the glycemic index (GI) is a measure of the relative impact of carbohydrate-containing foods on serum glucose. Consuming carbohydrates with a lower GI results in HbA1c reductions of 0.2% to 0.5% [23,24]. The differential effects of various carbohydrate sources on HbA1c in our study may be partly explained by the differences in the GI of each source. Since the GI of rice is higher than that of soft drinks or confectionery, it was expected that  $\Delta$ carbohydrate from rice would have a greater impact on  $\Delta$ HbA1c than that from soft drinks or confectionery. However, the results were opposite to this. Although the reasons are unclear, it is interesting that our results cannot be explained in terms of GI alone. They suggest that reducing carbohydrate from several sources would be more practical and useful than consuming foods with a lower GI.

Regarding  $\Delta$ carbohydrate from some sources (total fruits

and dairy in men; other wheat-based foods, sugar and sweeteners, soft drinks, and total alcoholic drinks in women), the results from analysis using Spearman's correlation coefficients were inconsistent with those from multiple regression analyses. One explanation is that this may have been due to outliers; however, there is the risk that eliminating some outliers would be arbitrary because outliers were not statistically defined. Another explanation is that although many patients usually consumed these sources, the mean reductions in them were very small (0.4 to 5.3 g/day). Further studies are needed for evaluating effects of the carbohydrate sources with small amounts or those with seasonal variations, like fruits, on HbA1c.

There were sex differences in the associations of reductions in various carbohydrate sources with decreases in HbA1c. Positive, moderate or weak correlations of  $\Delta$ carbohydrate from soft drinks, confectionery, rice, bread, and Chinese soup noodles with  $\Delta$ HbA1c were observed in men, while associations of  $\Delta$ carbohydrate from rice and confectionery with  $\Delta$ HbA1c were seen in women. These differences could be explained by differences in dietary habits between men and women. In women, there were only two carbohydrate sources that satisfied the two conditions of: a decrease in carbohydrate of more than 5.0 g/day after 6 months, the decrease after 6 months was statistically significant (rice and confectionery). In contrast, there were six carbohydrate sources that satisfied both of these conditions in men (rice, Chinese soup noodles, bread, confectionery, soft drinks, and beer).

The first strength of our study is that it included only patients with T2DM not taking any antidiabetic medications from 3 months before baseline to the end of study. Taking antidiabetic medication would lead to a mistaken understanding of net changes in HbA1c levels due to dietary therapy. Another strength is its use of dietary records to analyze intake from carbohydrate sources. The food frequency questionnaire or 24-hour recall frequently used in dietary management of T2DM have been less valid means of estimating amounts of carbohydrate intake compared with dietary records [25-27].

The first limitation of our study is that 3-day dietary records may not be enough for obtaining precise information about carbohydrate from sources that are not consumed as frequently as staple foods. Longer duration dietary records would be necessary. The second limitation is that the average level of carbohydrate intake at baseline in our patients was somewhat lower than in the general Japanese population [28]. They may already have been taking care regarding carbohydrate intake

before their first visit or they might have under-reported consumption of carbohydrate-rich foods in the dietary records. The third limitation is that we did not take changes in leisure-time physical activities into account. Data on changes in leisure-time physical activities during the 6 months were available only for 47 men and 36 women, about 1/3 of all patients. Although patients were requested to maintain their usual level of physical activity throughout the study, the 47 male patients increased their level of activity; however, there was no change for female patients. This number of patients is too small to conduct regression analysis. Thus, we need a further study to fully examine the confounding influence of changes in leisure-time physical activities in all patients. The fourth limitation is that our results will be valuable for patients with T2DM in East and Southern Asia where the major carbohydrate source is rice, but less so for patients in Western countries where the major carbohydrate source is not rice.

In summary, in 245 outpatients with T2DM not taking antidiabetic medications who followed a moderate low-carbohydrate diet for 6 months, focusing on the differential effects of carbohydrate sources on HbA1c, reducing carbohydrate from soft drinks, confectionery, bread, and Chinese soup noodles achieved a decrease in HbA1c that was 2- to 4-fold greater than that for the same reduction in rice in men, while reducing carbohydrate from confectionery achieved a decrease in HbA1c that was 2-fold greater in women. Dietary information provided to patients based on our results would enable them to reduce HbA1c efficiently.

## SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at <https://doi.org/10.4093/dmj.2020.0033>.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## AUTHOR CONTRIBUTIONS

Conception or design: H.H., S.W., K.M.

Acquisition, analysis, or interpretation of data: H.H., S.W., T.M., K.W.

Drafting the work or revising: H.H.

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