INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

A Non-calorie-restricted Low-carbohydrate Diet is Effective as an Alternative Therapy for Patients with Type 2 Diabetes

Yoshifumi Yamada, Junichi Uchida, Hisa Izumi, Yoko Tsukamoto,
Gaku Inoue, Yuichi Watanabe, Junichiro Irie and Satoru Yamada

Abstract

Objective Although caloric restriction is a widely used intervention to reduce body weight and insulin resistance, many patients are unable to comply with such dietary therapy for long periods. The clinical effectiveness of low-carbohydrate diets was recently described in a position statement of Diabetes UK and a scientific review conducted by the American Diabetes Association. However, randomised trials of dietary interventions in Japanese patients with type 2 diabetes are scarce. Therefore, the aim of this study was to examine the effects of a non-calorie-restricted, low-carbohydrate diet in Japanese patients unable to adhere to a calorie-restricted diet.

Methods The enrolled patients were randomly allocated to receive a conventional calorie-restricted diet or low-carbohydrate diet. The patients received consultations every two months from a registered dietician for six months. We compared the effects of the two dietary interventions on glycaemic control and metabolic profiles.

Results The HbA1c levels decreased significantly from baseline to six months in the low-carbohydrate diet group (baseline 7.6±0.4%, six months 7.0±0.7%, p=0.03) but not in the calorie-restricted group (baseline 7.7±0.6%, six months 7.5±1.0%, n.s.), (between-group comparison, p=0.03). The patients in the former group also experienced improvements in their triglyceride levels, without experiencing any major adverse effects or a decline in the quality of life.

Conclusion Our findings suggest that a low-carbohydrate diet is effective in lowering the HbA1c and triglyceride levels in patients with type 2 diabetes who are unable to adhere to a calorie-restricted diet.

Key words: calorie restriction, low-carbohydrate diet, type 2 diabetes

(Intern Med 53: 13-19, 2014)
(DOI: 10.2169/internalmedicine.53.0861)

Introduction

Type 2 diabetes is a worldwide pandemic that is accompanied by an obesity pandemic (1, 2). Visceral fat accumulation is a significant risk factor for the onset of metabolic syndrome and diabetes (3), and weight reduction is a recommended target for the first-line treatment and prevention of diabetes (4).

The American Diabetes Association (ADA) recommends that monitoring carbohydrate intake should be a component of diabetes therapy (4). Moreover, since 2008, the ADA has also recognised that low-carbohydrate diets, as well as calorie-restricted diets, are effective interventions for weight reduction (5). Notably, this recommendation differs from that reported in 2007, when the ADA did not recommend a carbohydrate intake of <130 g/day (6). Furthermore, Diabetes UK recently proposed that low-carbohydrate diets may also provide an effective treatment option (7), and the ADA reported the effectiveness of such diets for blood glucose and lipid management in a systematic review (8).

In contrast, the Japan Diabetes Society (JDS) currently recommends calorie restriction (25-35 kcal/kg of ideal body weight) for blood glucose management (9). Although calorie restriction has been confirmed to be effective for treating metabolic disorders, aging, carcinogenesis and dementia in

Diabetes Center, Kitasato Institute Hospital, Japan
Received for publication April 25, 2013; Accepted for publication July 25, 2013
Correspondence to Dr. Satoru Yamada, yamada-s@insti.kitasato-u.ac.jp

Rhesus monkeys (10), it may be difficult to adhere to such a diet for long periods.

Therefore, we examined the effectiveness of a non-calorie-restricted, low-carbohydrate diet for blood glucose and body weight management in Japanese patients with type 2 diabetes who were unable to adhere to a calorie-restricted diet.

Materials and Methods

Study design and subjects

This study was a single centre, 6-month, comparative, two-arm, randomised, open-label trial performed between April 1, 2011 and January 31, 2012. We recruited patients with type 2 diabetes who were being treated in our outpatient clinic who had received guidance regarding calorie restriction at least once and whose HbA1c level at enrolment was 6.9-8.4%, suggesting that their blood glucose level was not adequately controlled. Patients with proteinuria of >1.0 g/day, a serum creatinine level of >132 μmol/L (men) or 106 μmol/L (women), an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level of >3 times the upper limit of normal, a history of myocardial infarction or stroke within six months before study entry or an absolute change in the HbA1c of >1.0% within six months before study entry were excluded from this study. We avoided recruiting any patients with ketosis because ketoacidosis, which is a life-threatening complication, are reported during ketogenic low-carbohydrate diet (11, 12).

The enrolled patients were randomly allocated to receive either a non-calorie-restricted, low-carbohydrate diet (hereafter low-carbohydrate diet) or calorie-restricted diet using a permuted randomised block of four patients per block. The patients and investigators were not masked to group assignment. This study was undertaken in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice and was approved by our institutional review board (study ID 1010-02). Written informed consent was obtained from all enrolled patients.

Procedures

The enrolled patients were followed up at our outpatient clinic every two months. They received diet instructions at every medical consultation. During the study period, we did not change the medications, unless hypoglycaemia occurred. The HbA1c level, laboratory blood tests, body weight and incidence of hypoglycaemic episodes since the previous visit were recorded every two months. Dietary intake over the three days prior to each visit was also recorded.

The primary objective was to compare the reductions in the HbA1c level and body weight from baseline to the end of the 6-month treatment period between the two groups. The secondary efficacy variables included the lipid levels (total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) calculated using the Friedewald equation), blood pressure, markers of atherosclerosis (pulse-wave velocity (PWV), ankle-brachial pressure index (ABI) and toe-brachial pressure index (TBI)), the renal function (urinary nitrogen (UN), creatinine (Cr) and estimated glomerular filtration rate (eGFR), albumin-to-creatinine ratio (ACR)), the urinary albumin (UA) level and the levels of liver enzymes (AST, ALT and γ-glutamyl transpeptidase (γGTP)). To evaluate the effects of the diets on the quality of life, the patients completed the Diabetes Treatment Satisfaction Questionnaire (DTSQ) (13) and the Problem Areas In Diabetes (PAID) scale (14) at enrolment and at the end of the study.

The safety variables included adverse events reported by the patients or noted by the investigators, standard hematologic and blood chemistry tests, body weight and hypoglycaemia. Hypoglycaemia was defined as an event with typical symptoms (e.g., sweating, palpitations and feelings of hunger) with or without confirmation by a plasma glucose level of <70 mg/dL.

Meal instruction

Patients who were assigned to the calorie-restricted diet received face-to-face guidance on how to calculate their calorie intake by classifying macronutrients. The target calorie intake was defined based on the Japan Diabetes Society recommendations, as follows: total calorie intake (kcal) = ideal body weight (kg; =height (m) ×height (m) ×22) ×25. The target intake of specific macronutrients was as follows: carbohydrates=50-60%, protein=1.0-1.2 g/kg (<20%) and fat=<25% (9). For the low-carbohydrate diet, we set the total carbohydrate intake to be <130 g/day, as proposed by Accurso et al. (15). To prevent ketosis (11, 12, 16), we set the lower limit of carbohydrate intake to 70 g/day. To prevent postprandial hyperglycaemia, the target carbohydrate content in each meal was 20-40 g, and the subjects were allowed to consume sweets containing 5 g of carbohydrates twice daily, thus resulting in a total carbohydrate intake of 70-130 g/day. To avoid any possible influence of the experience and consulting skills of the dieticians in this study, four registered dieticians instructed the patients in both groups.

Sample size calculation

We estimated that the change in the HbA1c level over six months would be 0.0±0.5% in the calorie-restricted group and 0.7±0.5% in the low-carbohydrate group. We needed 22 patients, with α=0.05 and power=0.90. Therefore, we decided to enrol 24 patients in this study.

Statistical analysis

The results are presented as the mean±standard deviation. The Mann-Whitney U test was used for within-group and between-group comparisons. The Spearman's rank correlation test was used to assess the correlations between the carbohydrate or calorie intake and outcomes. Values of $p<0.05$ were considered to indicate a statistically significant differ-

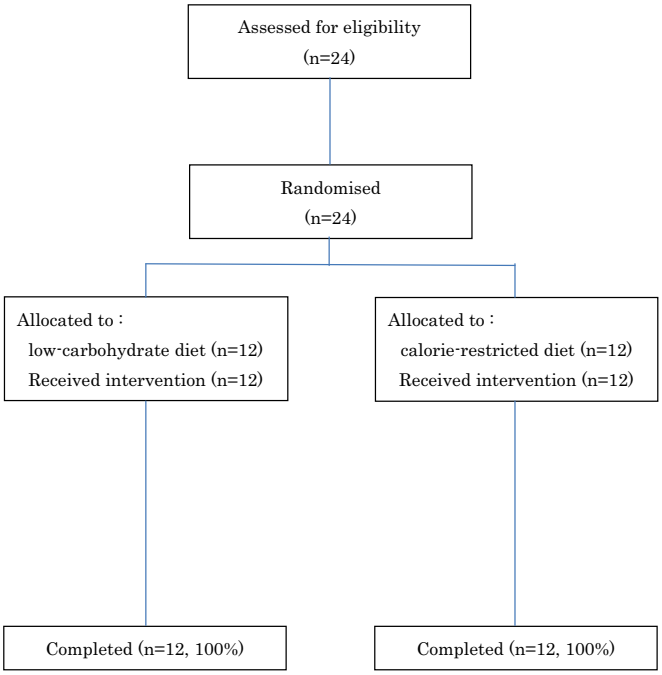

Figure 1. **Flow diagram of the patients.**

ence.

Results

Study population

The methodology of recruitment and screening is summarized in Fig. 1. A total of 24 patients with type 2 diabetes (mean age, 63.3±11.7 years; 50% women) who were being followed up at our outpatient clinic were enrolled and randomly allocated to receive either a low-carbohydrate diet or calorie-restricted diet. The general characteristics of the enrolled patients in each group are shown in Table 1. There were no statistically significant differences in any of the parameters between the two groups.

The low-carbohydrate diet improved the blood glucose levels and lipid levels (Table 2)

Six months after starting the diet, the HbA1c levels were significantly lower than those observed at baseline in the low-carbohydrate group (baseline 7.6±0.4%, six months 7.0±0.7%, p=0.03), whereas there were no changes in the HbA1c levels in the calorie-restricted group (baseline 7.7±0.6%, six months 7.5±1.0%, not significant (n.s.)) (Fig. 2a). The low-carbohydrate diet significantly improved the HbA1c levels in comparison with the calorie-restricted diet (p=0.03). The fasting plasma glucose levels were similar between baseline and at six months in both groups.

Body weight, BMI and blood pressure did not change significantly in either group.

In terms of the lipid levels, the TG levels significantly decreased in the low-carbohydrate group (baseline 141.7±76.2 mg/dL, six months 83.5±40.6 mg/dL, p=0.02), whereas no changes in the TG levels occurred in the calorie-restricted group (baseline 155.2±86.4 mg/dL, six months 148.4±90.7 mg/dL, n.s.) (Fig. 2b). However, the difference between the two groups was not statistically significant (p=0.08). The other markers of lipid profiles, the LDL-C levels and the HDL-C levels, were not altered in either group. Neither diet significantly affected markers of atherosclerosis, such as ABI, TBI and PWV.

Although we were concerned that excess protein intake may cause deterioration of the renal function in the low-carbohydrate group, we found no changes in the markers of the renal function (i.e., UN, Cr, eGFR and ACR) during the 6-month study in either group. A marker of the liver function, the ALT level, tended to improve in the low-carbohydrate group, likely due to the decrease in liver fat

Table 1. **Baseline Characteristics of the Patients Allocated to Each Diet**

	Low-carbohydrate diet	Calorie-restricted diet
Age (years)	63.3 ± 13.5	63.2 ± 10.2
Sex (male/female)	7/5	5/7
Duration of diabetes (years)	8.9 ± 3.6	9.5 ± 4.8
BMI (kg/m^2)	24.5 ± 4.3	27.0 ± 3.0
BW (kg)	67.0 ± 15.9	68.1 ± 7.7
HbA1c (NGSP) (%)	7.6 ± 0.4	7.7 ± 0.6
LDL-C (mg/dL)	99.8 ± 28.2	112.2 ± 20.5
TG (mg/dL)	141.7 ± 76.4	155.2 ± 86.4
HDL-C (mg/dL)	62.8 ± 17.1	59.8 ± 19.1
SBP (mmHg)	124.4 ± 10.8	124.9 ± 10.7
DBP (mmHg)	72.6 ± 6.2	74.8 ± 10.6
DTSQ total score (except items 2 and 3)	24.0 ± 6.6	21.6 ± 3.3
PAID score	42.1 ± 13.5	57.8 ± 12.6
Glucose-lowering drug ------no. (%)		
Insulin	3 (25.0)	4 (33.3)
Metformin	5 (41.7)	1 (8.3)
Sulfonylurea	5 (41.7)	8 (66.7)
Glinide	1 (8.3)	0 (0.0)
Thiazolidinedione	4 (33.3)	6 (50.0)
α-Glucosidase inhibitor	2 (16.7)	0 (0.0)
DPP-4 inhibitor	2 (16.7)	3 (25.0)
GLP-1	0 (0.0)	0 (0.0)
None	0 (0.0)	0 (0.0)
History of major microvascular disease		
Retinopathy		
None	10	10
SDR	0	2
PPDR	1	0
PDR	1	0
Nephropathy		
Stage 1	7	8
Stage 2	4	3
Stage 3A	1	1
Stage 3B, 4, 5	0	0

Values are means ± standard deviation.
There were no statistically significant differences between the two groups for any parameter.
BMI: body mass index, BW: body weight, HbA1c: haemoglobin A1c, NGSP: National Glycohemoglobin Standardization Program, LDL-C: low-density lipoprotein–cholesterol, TG: triglyceride, HDL-C: high-density lipoprotein–cholesterol, SBP: systolic blood pressure, DBP: diastolic blood pressure, DTSQ: Diabetes Treatment Satisfaction Questionnaire, PAID: Problem Areas In Diabetes scale, DPP: dipeptidyl peptidase, GLP: glucagon-like peptide, SDR: simple diabetic retinopathy, PPDR: pre proliferative diabetic retinopathy, PDR: proliferative diabetic retinopathy

Table 2. Efficacy Outcomes

Variable	Low-carbohydrate diet			Calorie-restricted diet			p value*
	Baseline	6 months	p value†	Baseline	6 months	p value†	
HbA1c NGSP (%)	7.6 ± 0.4	7.0 ± 0.7	0.03	7.7 ± 0.6	7.5 ± 1.0	n.s. (0.45)	0.03
FPG (mg/dL)	138 ± 44	124 ± 22	n.s. (0.40)	155 ± 46	163 ± 26	n.s. (0.42)	n.s. (0.33)
BW (kg)	67.0 ± 15.9	64.4 ± 14.2	n.s. (0.62)	68.1 ± 7.7	66.7 ± 7.0	n.s. (0.56)	n.s. (0.80)
BMI (kg/m^2)	24.5 ± 4.3	23.6 ± 3.5	n.s. (0.39)	27.0 ± 3.0	26.4 ± 2.2	n.s. (0.42)	n.s. (0.86)
LDL-C (mg/dL)	99.8 ± 28.2	95.2 ± 21.0	n.s. (0.77)	112.2 ± 20.5	110.5 ± 21.7	n.s. (0.77)	n.s. (0.49)
TG (mg/dL)	141.7 ± 76.2	83.5 ± 40.6	0.02	155.2 ± 86.4	148.4 ± 90.7	n.s. (0.58)	0.08
HDL-C (mg/dL)	62.8 ± 17.2	68.2 ± 22.1	n.s. (0.44)	59.8 ± 19.1	55.6 ± 13.9	n.s. (0.82)	n.s. (0.13)
SBP (mmHg)	124.4 ± 10.8	122.5 ± 11.9	n.s. (0.69)	124.9 ± 10.7	121.3 ± 11.6	n.s. (0.42)	n.s. (0.54)
DBP (mmHg)	72.6 ± 6.2	66.6 ± 9.4	n.s. (0.11)	74.8 ± 10.1	73.4 ± 10.1	n.s. (0.91)	n.s. (0.30)
PWV (cm/sec)	1,723.0 ± 213.8	1,788.8 ± 230.0	n.s. (0.60)	1,616.0 ± 162.9	1,626.3 ± 293.7	n.s. (0.77)	n.s. (0.69)
ABI	1.104 ± 0.093	1.153 ± 0.101	n.s. (0.24)	1.172 ± 0.085	1.187 ± 0.080	n.s. (0.44)	n.s. (0.36)
TBI	0.635 ± 0.265	0.644 ± 0.216	n.s. (0.54)	0.727 ± 0.134	0.707 ± 0.168	n.s. (0.80)	n.s. (0.91)
UN (mg/dL)	15.3 ± 3.1	17.1 ± 5.9	n.s. (0.47)	13.1 ± 3.4	14.0 ± 5.8	n.s. (0.77)	n.s. (0.77)
eGFR (mL/min/1.73m^2)	69.0 ± 14.5	69.4 ± 15.0	n.s. (0.71)	69.1 ± 13.2	65.0 ± 12.6	n.s. (0.33)	n.s. (0.39)
ACR (mg/gCr)	141.7 ± 322.1	96.8 ± 184.6	n.s. (0.69)	53.0 ± 93.0	131.5 ± 231.7	n.s. (0.89)	n.s. (0.21)
UA (mg/dL)	5.6 ± 1.3	5.7 ± 1.1	n.s. (0.69)	5.4 ± 1.0	5.4 ± 1.4	n.s. (0.69)	n.s. (0.69)
AST (U/L)	26.9 ± 7.6	24.1 ± 7.8	n.s. (0.36)	31.7 ± 17.1	34.7 ± 27.0	n.s. (0.77)	n.s. (0.29)
ALT (U/L)	28.6 ± 12.5	21.4 ± 5.9	0.07	32.4 ± 19.4	32.6 ± 17.5	n.s. (0.95)	n.s. (0.11)
γGTP (U/L)	38.5 ± 20.2	33.0 ± 16.4	n.s. (0.53)	35.8 ± 25.4	37.3 ± 33.7	n.s. (0.95)	n.s. (0.18)
DTSQ total score	24.0 ± 6.6	27.6 ± 5.7	n.s. (0.23)	21.6 ± 3.3	24.7 ± 4.5	0.07	n.s. (0.95)
DTSQ item 2: High BS	3.50 ± 1.68	2.42 ± 1.83	n.s. (0.13)	3.83 ± 0.94	3.67 ± 1.37	n.s. (0.77)	n.s. (0.21)
DTSQ item 3: Low BS	1.17 ± 1.90	1.42 ± 1.98	n.s. (0.95)	1.83 ± 1.53	1.75 ± 1.14	n.s. (0.98)	n.s. (0.31)
PAID score	42.1 ± 13.5	37.8 ± 11.3	n.s. (0.37)	57.8 ± 12.6	57.2 ± 11.9	n.s. (0.98)	n.s. (0.64)

*For between-group comparisons; †for within-group comparisons.
Values are means ± standard deviation.
HbA1c: haemoglobin A1c, n.s.: not significant, FBG: fasting blood glucose, BW: body weight, BMI: body mass index, NGSP: National Glycohemoglobin Standardization Program, LDL-C: low-density lipoprotein–cholesterol, TG: triglyceride, HDL-C: high-density lipoprotein–cholesterol, SBP: systolic blood pressure, DBP: diastolic blood pressure, PWV: pulse-wave velocity, ABI: ankle–brachial pressure index, TBI: toe–brachial pressure index, UN: urinary nitrogen, eGFR: estimated glomerular filtration index, ACR: albumin-to-creatinine ratio, UA: urinary albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γGTP: γ-glutamyl transpeptidase, DTSQ: Diabetes Treatment Satisfaction Questionnaire, BS: blood sugar, PAID: Problem Areas In Diabetes scale

content associated with the reduction in body weight. However, we did not assess the liver fat content using ultrasound or magnetic resonance spectrometry in this study.

Concerning the quality of life, the DTSQ score and the PAID score did not change in either group.

Taken together, these results indicate that the low-carbohydrate diet achieved greater improvements in the blood glucose and TG levels than the calorie-restricted diet. Particularly, the low-carbohydrate diet significantly improved the HbA1c levels in comparison with the calorie-restricted diet.

Three patients treated with a sulfonylurea or insulin in the low-carbohydrate group experienced symptomatic hypoglycaemia, although the events did not recur after adjusting the medications. None of the patients developed ketonuria during the study.

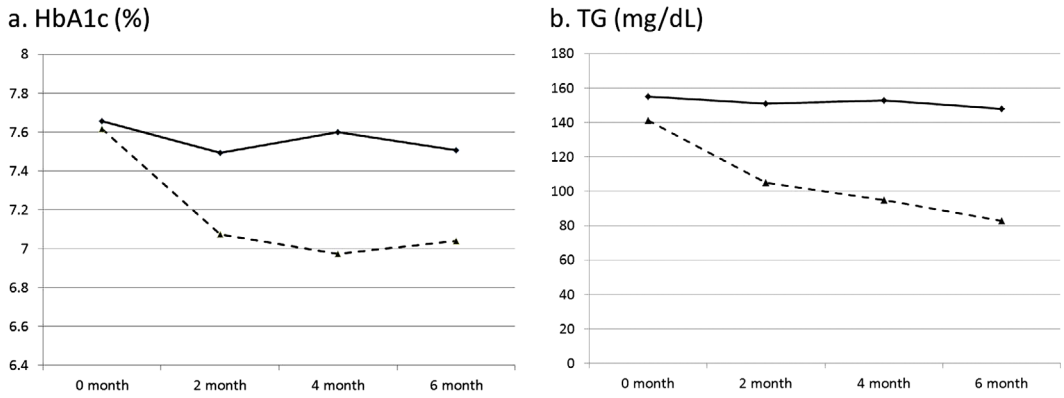

Figure 2. **Changes in the HbA1c (a) and triglyceride (b) levels during the 6-month intervention. Solid line: caloric restriction diet, dotted line: low-carbohydrate diet**

Table 3. **Nutrition Intake at 6 Months**

	Low-carbohydrate diet		Calorie-restricted diet		p value*
	Intake	Energy ratio (%)	Intake	Energy ratio (%)	
All patients					
Calorie intake (kcal)	1,634 ± 531	100	1,610 ± 387	100	n.s. (0.84)
Males					
Calorie intake (kcal)	1,891 ± 400		1,684 ± 526		n.s. (0.42)
Calorie intake/IBW	29.9 ± 6.7		27.2 ± 8.5		n.s. (0.68)
Females					
Calorie intake (kcal)	1,274± 507		1,557 ± 286		n.s. (0.22)
Calorie intake/IBW	24.1±10.7		30.3 ± 5.2		n.s. (0.17)
Intake of specific nutrients					
Protein (g)	100.4 ± 36.6	25.3 ± 7.3	67.6 ± 21.2	16.6 ± 2.8	0.021
Protein/BW	1.592 ± 0.573		1.022 ± 0.329		0.009
Fat (g)	82.1 ± 33.0	45.4 ± 8.9	58.5 ± 20.7	32.3 ± 5.2	0.028
Carbohydrate (g)	125.7 ± 71.9	29.8 ± 12.5	202.9 ± 42.0	51.0 ± 4.6	0.008
Salt (g)	10.2 ± 2.5		10.4 ± 2.4		n.s. (0.30)

*For between-group comparisons.
Values are means ± standard deviation.
n.s.: not significant, IBW: ideal body weight, BW: body weight

Nutrient intake at six months

Although we did not prescribe calorie restriction to the patients assigned to the low-carbohydrate group, the calorie intake at six months was actually similar in both groups (Table 3). Stratified by sex, the calorie intake in the low-carbohydrate group tended to be higher in men and lower in women compared with that observed in the calorie-restricted group. The relative nutrient intake of carbohydrates, protein and fat was 29.8±12.5%, 25.3±7.3% and 45.4±8.9% in the low-carbohydrate group, compared with 51.0±4.6%, 16.6± 2.8% and 32.3±5.2%, respectively, in the calorie-restricted group. The carbohydrate intake was significantly lower in the low-carbohydrate group than in the calorie-restricted group. The mean carbohydrate intake in the low-carbohydrate group was <130 g/day, suggesting that most patients were able to adhere to the meal instructions.

Correlations between carbohydrate or calorie intake and outcomes

We next performed correlation analyses in 10 patients with nutrient intake data both at baseline and at the end of the study (five patients in each group). In these patients, we found that the change in body weight was significantly correlated with the change in carbohydrate intake (r=0.764, p= 0.0078) and the change in calorie intake (r=0.769, p= 0.0071). The change in the HbA1c level was significantly correlated with the change in carbohydrate intake (r=0.670, p=0.0321) but not with the change in calorie intake (r= 0.439, n.s.).

Discussion

In this randomised study, we examined whether a non-calorie-restricted, low-carbohydrate diet is effective and safe in Japanese patients with type 2 diabetes and inadequate glycaemic control while on a calorie-restricted diet. Significant improvements in the HbA1c level were observed in the low-carbohydrate group but not in the calorie-restricted group. Overall, these findings are compatible with the recommendations of the ADA (4, 5, 8) and Diabetes UK (7).

We also found improvements in the TG levels in the low-

carbohydrate group. Two previous meta-analyses, which included five trials (17) and 13 trials (18), respectively, showed worsening of the TC and LDL-C levels and improvements in the TG and HDL-C levels with a low-carbohydrate diet. However, another meta-analysis of 22 trials showed no deterioration in the TC or LDL-C levels and significant improvements in the TG and HDL-C levels with a low-carbohydrate diet (19). Consistent with that report, we found improvements in the TG levels without deterioration in the TC or LDL-C levels. Therefore, a low-carbohydrate diet appears to have beneficial effects on lipid profiles as well as glycaemic control.

The ADA recommends monitoring the renal function and protein intake, particularly in patients with nephropathy, during low-carbohydrate dietary interventions in addition to monitoring lipid profiles (4, 5). Although the subjects in the low-carbohydrate group consumed less carbohydrates, more protein and more fat than those in the calorie-restricted group, the renal function did not deteriorate in the former group. The protein intake in the low-carbohydrate group in this study was 1.6±0.6 g/kg. Although the Japanese Reference Diet Intake report 2010 recommended an upper limit of protein intake of 2.0 g/kg (20) based on data from critically ill patients, critically ill patients should be allowed to receive undernutrition (21) and the Dietary Reference Intake in the US has no upper limit for protein intake (22).

Although a previous report claimed that atherosclerosis may be caused by a low-carbohydrate diet (23), we did not observe cerebrovascular end points due to the short observation period. There was no deterioration in the levels of markers of atherosclerosis (i.e., ABI, TBI and PWV) in the low-carbohydrate group. It is necessary to evaluate the long-term safety of low-carbohydrate diets for atherosclerosis carefully in the future.

Although we did not limit calorie intake in the low-carbohydrate diet group, the calorie intake at six months after the intervention was almost equal in both groups. In the low-carbohydrate diet group, the patients ate protein and fat, such as meat or fish, in substitution of carbohydrates. As a result, the quantity of the meal increased and the patients may therefore more easily feel full. In addition, lightly seasoned staple foods (such as rice, bread, noodles and so on), which are rich in carbohydrates, may promote overeating of strongly seasoned side dishes (such as meat, fish and so on), and it may be difficult to frequently eat only side dishes. On the other hand, because all enrolled patients had previously received guidance on calorie restriction at least once, we cannot deny the possibility that the patients allocated to the low-carbohydrate diet group limited not only the carbohydrate volume, but also the calorie intake under the influence of former meal instruction.

There are several limitations to this study that should be discussed. First, the number of subjects enrolled was too small to detect significant differences in the between-group and within-group comparisons. Santos et al. reviewed 23 reports, consisting of 1,141 patients in total, concerning the effects of low-carbohydrate diets and reported that low-carbohydrate diets are clearly associated with significant decreases in body weight, BMI, abdominal circumference, systolic blood pressure, diastolic blood pressure, plasma TG, fasting plasma glucose, glycated haemoglobin, plasma insulin and plasma CRP as well as increases in HDL-C (24). We did not observe any significant improvements in body weight, BMI, blood pressure or HDL-C in this study; however, increasing the number of subjects may prove the significant effectiveness of low-carbohydrate diets in improving these parameters. Second, this was a 6-month study. Several clinical trials of low-carbohydrate diets have shown small or moderate rebounds in clinical parameters between six months and 12 months after starting the intervention (25, 26). Therefore, the improvements in the HbA1c levels and body weight observed at six months in our study may be attenuated over a longer observation period.

In conclusion, we found that a non-calorie-restricted, low-carbohydrate diet is effective in lowering the HbA1c and TG levels and is safe as an alternative therapy for patients with type 2 diabetes. Because the number of subjects enrolled was small and the study duration was short, longer multicentre studies with a larger sample size are needed to confirm our findings.

The authors state that they have no Conflict of Interest (COI).

References

1. The diabetes pandemic. Lancet **378**: 99, 2011.
2. Ramachandran A, Ma RC, Sneharatha C. Diabetes in Asia. Lancet **375**: 408-418, 2010.
3. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome: a new worldwide definition. Lancet **366**: 1059-1062, 2005.
4. American Diabetes Association. Standards of medical care in diabetes 2012. Diabetes Care **35**: S11-S63, 2012.
5. American Diabetes Association. Nutrition recommendations and interventions for diabetes. Diabetes Care **31**: S61-S78, 2008.
6. American Diabetes Association. Nutrition recommendations and interventions for diabetes. Diabetes Care **30**: S48-S65, 2007.
7. Dyson PA, Kelly T, Deakin A, et al. Diabetes UK evidence-based nutrition guidelines for the prevention and management of diabetes. Diabet Med **28**: 1282-1288, 2011.
8. Wheeler ML, Dunbar SA, Jaacks LM, et al. Macronutrients, food groups, and eating patterns in the management of diabetes: a systematic review of the literature, 2010. Diabetes Care **35**: 434-445, 2012.
9. Japan Diabetes Society. Diet therapy. In: Treatment Guide for Diabetes 2012-2013. Bunkodo, Tokyo, 2012: 39-42 (in Japanese).
10. Colman RJ, Anderson RM, Johnson SC, et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. Science **325**: 201-204, 2009.
11. Chen TY, Smith W, Rosenstock JL, Lessnau KD. A life-threatening complication of Atkins diet. Lancet **367**: 958, 2006.
12. Shah P, Isley WL. Ketoacidosis during a low-carbohydrate diet. N Engl J Med **354**: 97-98, 2006.
13. Bradley C. Diabetes Treatment Satisfaction Questionnaire. Change version for use alongside status version provides appropriate solution where ceiling effects occur. Diabetes Care **22**: 530-532, 1999.
14. Welch GW, Jacobson AM, Polonsky WH. The Problem Areas in

Diabetes Scale. An evaluation of its clinical utility. Diabetes Care **20**: 760-766, 1997.

15. Accurso A, Bernstein RK, Dahlgvist A, et al. Dietary carbohydrate restriction in type 2 diabetes mellitus and metabolic syndrome: time for a critical appraisal. Nutr Metab (Lond) **5**: 9, 2008.

16. Westman EC, Feinman RD, Mavropoulos JC, et al. Low-carbohydrate nutrition and metabolism. Am J Clin Nutr **86**: 276-284, 2007.

17. Nordmann AJ, Nordmann A, Briel M, et al. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors. Arch Intern Med **166**: 285-293, 2006.

18. Hession M, Rolland C, Kulkarni U, Wise A, Broom J. Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities. Obes Rev **10**: 36-50, 2009.

19. Kodama S, Saito K, Tanaka S, et al. Influence of fat and carbohydrate proportions on the metabolic profile in patients with type 2 diabetes: a meta-analysis. Diabetes Care **32**: 959-965, 2009.

20. Ministry of Health, Labour, and Welfare, Japan. Protein, in Dietary Reference Intakes for Japanese 2010. Daiichi Shuppan Publishing Co., Tokyo, 2010: 62-76 (in Japanese).

21. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med **365**: 506-517, 2011.

22. Institute of Medicine of the National Academies. Protein and Amino Acids, in Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. The National Academies Press, Washington DC, 2005: 589-768.

23. Smith SR. A look at the low-carbohydrate diet. N Engl J Med **361**: 2286-2288, 2009.

24. Santos FL, Esteves SS, da Costa Pereira A, Yancy WS Jr, Nunes JP. Systematic review and meta-analysis of clinical trials of the effects of low carbohydrate diets on cardiovascular risk factors. Obes Rev **13**: 1048-1066, 2012.

25. Shai I, Schwarzfuchs D, Henkin Y, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med **359**: 229-241, 2008.

26. Gardner CD, Kiazand A, Alhassan S, et al. Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. JAMA **297**: 969-977, 2007.