ORIGINAL ARTICLE

Association between low-carbohydrate diets and continuous glucose monitoring-derived time in ranges

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ABSTRACT

Aims: Low-carbohydrate diets have become popular in the general community. The mutual relationship between the percentage of total energy intake from carbohydrates (CHO/E), glycemic control indices, and diabetes complications remains unclear.

Materials and Methods: This cross-sectional study included 177 patients with type 2 diabetes mellitus who regularly visited outpatient clinics. In this study, dietary questionnaires were used to assess the intake ratio of the three macronutrients, and the low-carbohydrate-diet score was calculated. We investigated the association between the low-carbohydrate-diet score, continuous glucose monitoring (CGM)-derived short-term glycemic control indices, and diabetes complications in patients with type 2 diabetes mellitus.

Results: The results are presented as medians (interquartile ranges) unless otherwise stated. Hemoglobin A1c was 7.1% (6.6–7.7%), CGM-derived time in range (TIR) was 75.3% (62.8–87.0%), body mass index (BMI) was 24.0 (22.1–26.3) kg/m^2, and CHO/E was 49.8% (44.8–55.6%). BMI, triglycerides, and CGM-derived time above range decreased significantly with increasing low-carbohydrate-diet scores. However, no significant association was found between the low-carbohydrate-diet score and glycemic control indices, including TIR, mean amplitude of glycemic excursions, and vascular complications of type 2 diabetes mellitus.

Conclusion: Moderate-carbohydrate diets positively impact weight control and lipid metabolism but may have a limited effect on short-term glycemic variability in Japanese patients with type 2 diabetes mellitus.

INTRODUCTION

The purpose of medical nutrition therapy for type 2 diabetes mellitus is to correct metabolic abnormalities caused by hyperglycemia and to prevent the onset and progression of the chronic complications of diabetes. Medical nutrition therapy plays a significant role in the treatment of type 2 diabetes mellitus. In Japan, it is recommended that the total energy intake or the dietary nutrient ratios for each patient should be determined flexibly, taking into account patient factors such as the patient's physical activity level, comorbidities, age, and preferences.[1]

Low-carbohydrate (carbohydrate-restricted) diets, which restrict carbohydrate consumption relative to the general diet, have become increasingly popular for weight loss. Furthermore, low-carbohydrate diets have been shown to have beneficial effects on cardiovascular risk factors, including triglycerides (TG), and are useful for short-term hemoglobin A1c (HbA1c) deterioration in patients with type 2 diabetes mellitus[2–4]. However, the long-term efficacy of low-carbohydrate diets remains unclear. Low-carbohydrate diets

typically consist of 60–130 g/day of carbohydrates (26–45% of total daily energy intake). Conversely, some reports defined a low-carbohydrate diet as <130 g/day of carbohydrate intake or <26% of the total daily energy intake, a moderate-carbohydrate diet as 26–45% of the total daily energy intake, and a high-carbohydrate diet as >45% of the total daily energy intake[5,6]. Thus, there is no clear definition of the carbohydrate ratio of a low-carbohydrate diet, and evaluating its usefulness is known to be challenging.

Dietary questionnaires have been used to assess nutrients in the diet. Some studies have reported a positive correlation between the percentage of total energy intake in the form of carbohydrates (CHO/E) calculated from dietary questionnaires and HbA1c[7], whereas others found no association[8]. The low-carbohydrate-diet score has been reported to be a useful indicator for evaluating low-carbohydrate diets[9]. The low-carbohydrate-diet score is also reportedly associated with cardiovascular events and total mortality[10,11].

Glycemic variability (GV) is associated with chronic complications of diabetes through worsening oxidative stress and increased risk of hypoglycemia[12]. Indeed, oxidative stress markers are associated with continuous glucose monitoring (CGM)-derived GV indices[13,14]. CGM-derived time in range (TIR) is becoming widely used as a glycemic control index in daily clinical practice[15]. Time in range has been reported to be associated not only with the development and progression of diabetic microvascular complications but also with cardiovascular death[16–21].

While there are various reports on the association between CHO/E and HbA1c[2–4,7,8], the association between low-carbohydrate diets and CGM-derived GV indices and time in range remains unknown. Furthermore, the relationship between low-carbohydrate diets and diabetes complications remains unclear. This study aimed to examine the relationship between the low-carbohydrate-diet score, CGM-derived glycemic control indices, and diabetes chronic complication indicators, including urine albumin–creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), and brachial–ankle pulse wave velocity (ba-PWV).

METHODS

Study design and participants
This cross-sectional analysis was conducted as part of the Hyogo Diabetes Hypoglycemia Cognition Complications (HDHCC) study[20]. The HDHCC study is a multicenter prospective cohort study that aims to investigate the relationship between blood glucose control and chronic diabetes complications in patients with type 2 diabetes mellitus who visited outpatient clinics with diabetologists. The present study included patients with type 2 diabetes mellitus aged between 40 and 81 years who completed a dietary questionnaire and regularly visited outpatient clinics at Hyogo Medical University Hospital or Kusunoki Clinic. The following were the exclusion criteria: (i) participants unable to regularly attend the clinic or

hospital, (ii) those in whom CGM data could not be obtained for >7 consecutive days, (iii) those with severe hepatic impairment, (iv) those with severe renal dysfunction, (v) those diagnosed with dementia, (vi) those with self-reported total energy intake of <600 kcal/day or >4,000 kcal/day[22], and (vii) those deemed ineligible for the present study by their attending physician.

This study was approved by the Ethics Committee of Hyogo Medical University Hospital (Approval No. 0390), and all participants signed informed consent forms.

Calculation of the low-carbohydrate-diet score
The brief-type self-administered diet history questionnaire (BDHQ) was used to examine quantitatively the participants' nutrient and food intake during the past month[23,24]. The low-carbohydrate-diet score computation was reported previously[9]. In brief, participants were divided into 11 strata based on protein, fat, and carbohydrate intake expressed as a percentage of energy, respectively (Table S1). For example, for protein and fat intakes, the highest group scored 10 points, the second highest group scored 9 points, and the lowest group scored 0 points. For carbohydrates, the order of the strata was reversed; those with the lowest carbohydrate intake scored 10 points, and those with the highest carbohydrate intake scored 0 points. The low-carbohydrate-diet score was calculated as the sum of the total points for carbohydrate, protein, and fat. The low-carbohydrate-diet score was calculated using percentages of energy intake rather than absolute intake to reduce bias due to under-reporting of food intake and represent dietary composition[9].

CGM
In this study, each participant was instructed to wear the Free-Style Libre Pro® (Abbott Japan, Tokyo, Japan) for 14 days, and all sensor glucose (SG) data obtained were used. The GV indices calculated from the obtained CGM data were as follows: (i) standard deviation (SD), (ii) coefficient of variation (CV), (iii) mean amplitude of glycemic variability (MAGE), and (iv) continuous overlapping net glycemic action calculated every 1 h (CONGA-1 h). In addition, the following other glycemic control indicators other than GV indices were calculated: (i) mean sensor glucose, (ii) high blood glucose index (HBGI), (iii) low blood glucose index (LBGI), (iv) the time spent with sensor glucose values in the range of 70–180 mg/dL (TIR_{70-180}), (v) the time spent with sensor glucose values higher than 180 mg/dL (time above range; $TAR_{>10}$), and (vi) the time spent sensor glucose values below 70 mg/dL (time below range; TBR).

Blood sampling, urinalysis, and PWV measurement
HbA1c, UACR, eGFR, and each patient's background were investigated at the time of wearing the CGM device. The ba-PWV was measured using BP-203RPE III (Fukuda Colin, Tokyo, Japan) at the time of attaching the CGM device.

Statistical analysis

The results are presented as medians (interquartile ranges) unless otherwise stated. The participants were divided into quadrants based on their low-carbohydrate-diet scores. The Jonckheere–Terpstra test was used to compare trends in the data among the four groups. In addition, the Cochran–Armitage test was used to compare the trend of the ratio between the four groups.

High BMI was defined as a value greater than the median (BMI >24.0 kg/m^2), and high triglycerides as ≥150 mg/dL[25]. The receiver operating characteristic (ROC) curve was used to analyze the low-carbohydrate-diet score to identify the cutoff values that predict high BMI and high triglycerides. The area under the curve was calculated from the ROC curve, and an appropriate cutoff value was calculated based on the Youden index. According to the Dietary Reference Intakes for Japanese (2020 edition), zinc intake of ≥11 mg/day for men 18–74 years of age, ≥10 mg/day for men ≥75 years of age, and ≥8 mg/day for women ≥18 years of age is recommended[26]. An ROC analysis was performed to determine the optimal thresholds for the low-carbohydrate-diet score and zinc intake in patients with type 2 diabetes mellitus.

The BellCurve software Ver. 4.03 (Social Research and Information Center, Tokyo, Japan) was used for statistical analysis in this study, and a value of P of less than 0.05 was considered statistically significant.

RESULTS

Clinical characteristics of the participants

Of the 252 patients with type 2 diabetes mellitus who participated in the questionnaire-based nutrition survey from May 2018 to July 2022, 206 responses were received. Of the participants, 25 were excluded because CGM data were not available for more than 7 consecutive days. In addition, one patient whose self-reported energy intake of <600 kcal/day was excluded and three were excluded due to renal dysfunction. Finally, 177 participants (55 females and 122 males) with the median age of 68 (63–72) years and median body mass index (BMI) of 24.0 (22.1–26.3) kg/m^2 were analyzed in the present study. The CHO/E and the percentage of total energy intake from protein (P/E) and total fat (F/E) of all participants were 49.8% (44.8–55.6%), 15.9% (13.8–18.2%), and 28.3% (24.1–32.6%), respectively.

Differences in nutrients based on the low-carbohydrate-diet score

The participants' characteristics divided into quartiles based on the low-carbohydrate-diet score are shown in Table 1. There were no significant differences in sex (P for trend = 0.317) and age (P = 0.674) among the four groups. Conversely, the BMI (P for trend = 0.043) tended to decrease with increasing low-carbohydrate-diet scores. We constructed an ROC curve for predicting high BMI for the low-carbohydrate-diet score (Figure S1). As a result, the low-carbohydrate-diet score of 12

points was determined as the threshold [area under the receiver operator characteristic curve (AUROC) = 0.591; sensitivity = 48.3%; specificity = 69.3%; P = 0.034].

Differences in the total daily energy intake and nutrient ratios were investigated based on the low-carbohydrate-diet score. There was no significant difference in the total daily energy intake (P for trend = 0.419) among the four groups. The CHO/E tended to decrease, whereas P/E and F/E tended to increase with increasing low-carbohydrate-diet scores (all P for trend <0.001). Moreover, not only the saturated fatty acid-to-energy ratio (SFA/E) but also the monounsaturated fatty acid-to-energy ratio (MUFA/E) and polyunsaturated fatty acid-to-energy ratio (PUFA/E) tended to increase following the increase in the low-carbohydrate-diet score (all P for trend <0.001).

Next, the relationship between the low-carbohydrate-diet score and trace element intake was examined. The daily intake of zinc, iron, and phosphorus tended to increase with increasing low-carbohydrate-diet scores (all P for trend <0.001).

Differences in GV and TIR based on the low-carbohydrate-diet score

There was no significant association between the low-carbohydrate-diet score and HbA1c (P for trend = 0.104) or duration of type 2 diabetes mellitus (P for trend = 0.127; Table 2). Furthermore, no significant association between the low-carbohydrate-diet score and the prescription status of each diabetes medication was observed.

The association between the low-carbohydrate-diet score and CGM metrics is shown in Figures 1 and 2. In addition, the median and interquartile range curves of glucose values obtained from CGM are shown in Figure 3. TAR$_{>180}$ (P for trend = 0.017) and HBGI (P for trend = 0.021) showed a tendency to increase with increasing low-carbohydrate-diet scores. In contrast, no association between the low-carbohydrate-diet score and TIR$_{70-180}$ was noted (P for trend = 0.079).

While CV (P for trend = 0.033) tended to increase with increasing low-carbohydrate-diet scores, no association between the low-carbohydrate-diet score and SD (P for trend = 0.266) or LBGI (P for trend = 0.098) was observed. Moreover, no association between the low-carbohydrate-diet score and MAGE (P for trend = 0.299) or continuous overlapping net glycemic action calculated every 1 h (P for trend = 0.431) was noted.

Differences in clinical parameters based on the low-carbohydrate-diet score

The proportions of patients administered various classes of diabetes medications were compared across the four groups (Table 2). There were no statistically significant differences between the four groups in the proportion of patients based on their diabetes medications, which included SGLT2 inhibitors implicated in glucose excretion (P for trend = 0.499). The relationship between the low-carbohydrate-diet score and lipid profiles and blood pressure is presented in Table 3. There was no significant association between the low-carbohydrate-diet score

Table 1 | Participant characteristics

	Q1 (N = 45)	Q2 (N = 47)	Q3 (N = 44)	Q4 (N = 41)	P for trend
Female	13 (28.9%)	12 (25.5%)	15 (34.1%)	15 (36.6%)	0.317
Low-carbohydrate-diet score	5.0 (2.0–7.0)	12.0 (11.0–13.5)	19.0 (17.0–21.0)	26.0 (23.0–27.0)	<0.001
Age, years old	68 (63–72)	67 (62–71)	69 (65–71)	68 (64–71)	0.674
BMI, kg/m^2	24.0 (22.6–25.5)	24.9 (22.7–27.4)	24.1 (22.2–26.0)	23.1 (21.3–25.1)	0.043
Current smoker, N (%)	8 (17.8%)	9 (19.1%)	11 (25.0%)	5 (12.2%)	0.733
Total energy, kcal/day	1743.3 (1229.5–2049.4)	1688.8 (1419.4–2191.1)	1956.6 (1551.9–2361.9)	1698.3 (1233.1–1987.7)	0.419
Macronutrient intake, % of energy					
Carbohydrate	60.7 (58.0–63.3)	53.1 (48.5–55.3)	48.7 (46.9–50.1)	43.8 (41.5–45.4)	<0.001
Protein	13.3 (11.8–14.0)	15.0 (13.8–16.8)	16.8 (15.2–18.5)	20.0 (18.3–21.8)	<0.001
Total fat	22.4 (17.9–24.1)	27.3 (24.7–28.4)	31.5 (28.8–32.9)	34.7 (32.2–36.9)	<0.001
Saturated fat	5.3 (4.4–6.5)	7.2 (5.9–7.9)	8.1 (7.4–9.3)	8.7 (8.4–9.6)	<0.001
Monounsaturated fat	7.9 (6.2–8.6)	9.6 (8.4–10.4)	11.4 (10.0–12.1)	12.3 (11.1–13.3)	<0.001
Polyunsaturated fat	5.3 (4.7–5.9)	6.6 (5.8–7.1)	7.4 (6.6–8.2)	8.6 (8.0–9.5)	<0.001
Total dietary fiber, g/day	10.1 (8.5–12.8)	11.1 (8.8–13.5)	13.1 (11.3–16.3)	14.3 (9.3–17.9)	<0.001
Sodium chloride, g/day	9.1 (7.4–11.8)	9.9 (8.5–12.9)	12.5 (10.2–15.1)	10.8 (8.5–14.6)	0.001
Alcohol, g/day	0 (0–13.9)	1.2 (0–25.0)	2.2 (0–9.6)	0.2 (0–3.5)	0.993
Copper, mg/day	1.0 (0.8–1.3)	1.0 (0.8–1.2)	1.2 (1.0–1.4)	1.2 (0.8–1.4)	0.024
Zinc, mg/day	6.6 (5.4–8.1)	7.2 (5.7–9.0)	9.2 (6.4–10.8)	8.9 (6.8–10.0)	<0.001
Iron, mg/day	6.5 (4.9–7.8)	7.3 (6.0–9.1)	9.4 (7.4–11.3)	10.0 (7.3–11.6)	<0.001
Manganese, mg/day	3.3 (2.3–4.1)	3.3 (2.3–4.0)	3.6 (3.0–4.5)	3.1 (2.5–3.7)	0.287
Phosphorus, mg/day	836.8 (659.5–980.3)	998.9 (789.9–1221.3)	1260.3 (985.1–1583.3)	1264.0 (895.5–1491.2)	<0.001
Calcium, mg/day	383.8 (325.9–471.8)	539.8 (388.8–690.6)	683.4 (562.4–857.3)	681.7 (529.3–830.2)	<0.001
Vitamin D, μg/day	7.2 (4.9–12.1)	12.7 (9.0–20.4)	18.3 (12.2–27.4)	16.4 (10.2–26.6)	<0.001
Magnesium, mg/day	213.5 (169.1–264.2)	237.6 (191.1–295.8)	291.9 (236.1–355.7)	309.0 (217.6–346.1)	<0.001

The results are presented as medians (interquartile ranges). The participants were divided into quadrants based on the low-carbohydrate-diet score. Clinical parameters among quadrants were examined using the Jonckheere–Terpstra test or Cochran–Armitage test. BMI, body mass index.

Table 2 | Differences in diabetes treatment status based on the low-carbohydrate-diet score

|	Q1 (N = 45)	Q2 (N = 47)	Q3 (N = 44)	Q4 (N = 41)	P for trend
HbA1c, %	7.3 (6.7–8.2)	7.4 (6.6–7.9)	7.0 (6.6–7.3)	7.0 (6.7–7.4)	0.104
GA, %	18.7 (17.0–21.4)	18.2 (16.1–20.2)	18.0 (16.1–19.6)	18.5 (16.3–20.9)	0.202
Disease duration, years	12 (7–21)	13 (7–20)	14 (10–25)	15 (10–22)	0.127
Antihyperglycemic drugs					
Insulin, N (%)	11 (24.4%)	11 (23.4%)	15 (34.1%)	14 (34.1%)	0.192
GLP-1 RAs, N (%)	5 (11.1%)	5 (10.6%)	5 (11.4%)	6 (14.6%)	0.620
DPP-4Is, N (%)	25 (55.6%)	26 (55.3%)	17 (38.6%)	22 (53.7%)	0.465
SGLT-2is, N (%)	12 (26.7%)	14 (29.8%)	13 (29.5%)	8 (19.5%)	0.499
Metformin, N (%)	23 (51.1%)	26 (55.3%)	23 (52.3%)	17 (41.5%)	0.369
Thiazolidines, N (%)	4 (8.9%)	2 (4.3%)	3 (6.8%)	2 (4.9%)	0.565
α-GIs, N (%)	7 (15.6%)	5 (10.6%)	7 (15.9%)	3 (7.3%)	0.408
Sulfonylureas or glinides, N (%)	14 (31.1%)	10 (21.3%)	12 (27.3%)	9 (22.0%)	0.472

The results are presented as medians (interquartile ranges). The participants were divided into quadrants based on the low-carbohydrate-diet score. Clinical parameters among quadrants were examined using the Jonckheere–Terpstra test or Cochran–Armitage test. DPP-4Is, dipeptidyl peptidase-4 inhibitors; GA, glycated albumin; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; SGLT-2is, sodium-glucose cotransporter-2 inhibitors; α-GIs, α-glucosidase inhibitors.

and the use of dyslipidemia medication (P for trend = 0.971). High-density lipoprotein (HDL) cholesterol (P for trend = 0.003) tended to increase, whereas triglycerides (P for trend <0.001) tended to decrease with increasing low-carbohydrate-diet scores.

The ROC analysis also calculated the low-carbohydrate-diet score of 17 as the threshold for predicting hypertriglyceridemia (AUROC = 0.678; sensitivity = 82.6%; specificity = 47.3%; P < 0.001).
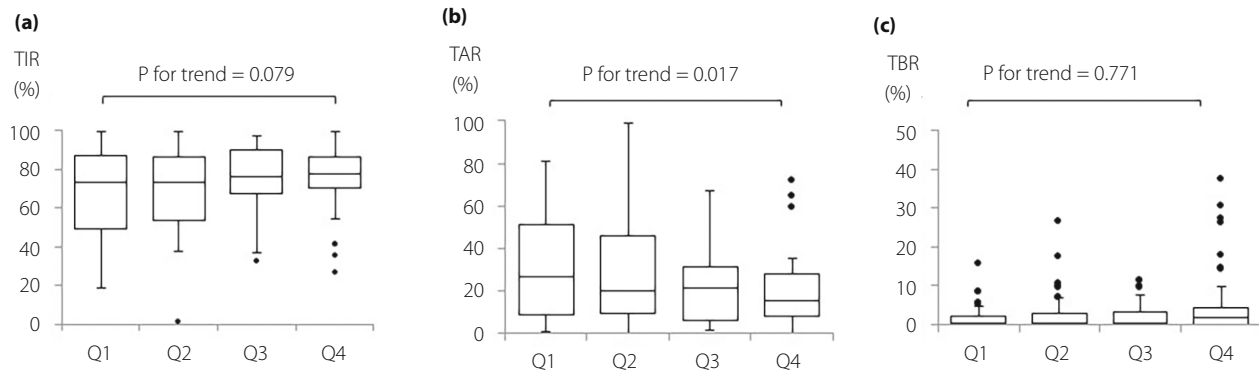
Figure 1 | Association between the low-carbohydrate-diet score and time in ranges derived from continuous glucose monitoring. (a) Time in range 70–180 mg/dL (TIR_{70-180}), (b) time above range >180 mg/dL ($TAR_{>180}$), and (c) time below range <70 mg/dL ($TBR_{<70}$). Data are shown in box and whisker plots using the Tukey method. The black dots are outliers. Q1, quadrant 1; Q2, quadrant 2; Q3, quadrant 3; Q4, quadrant 4.
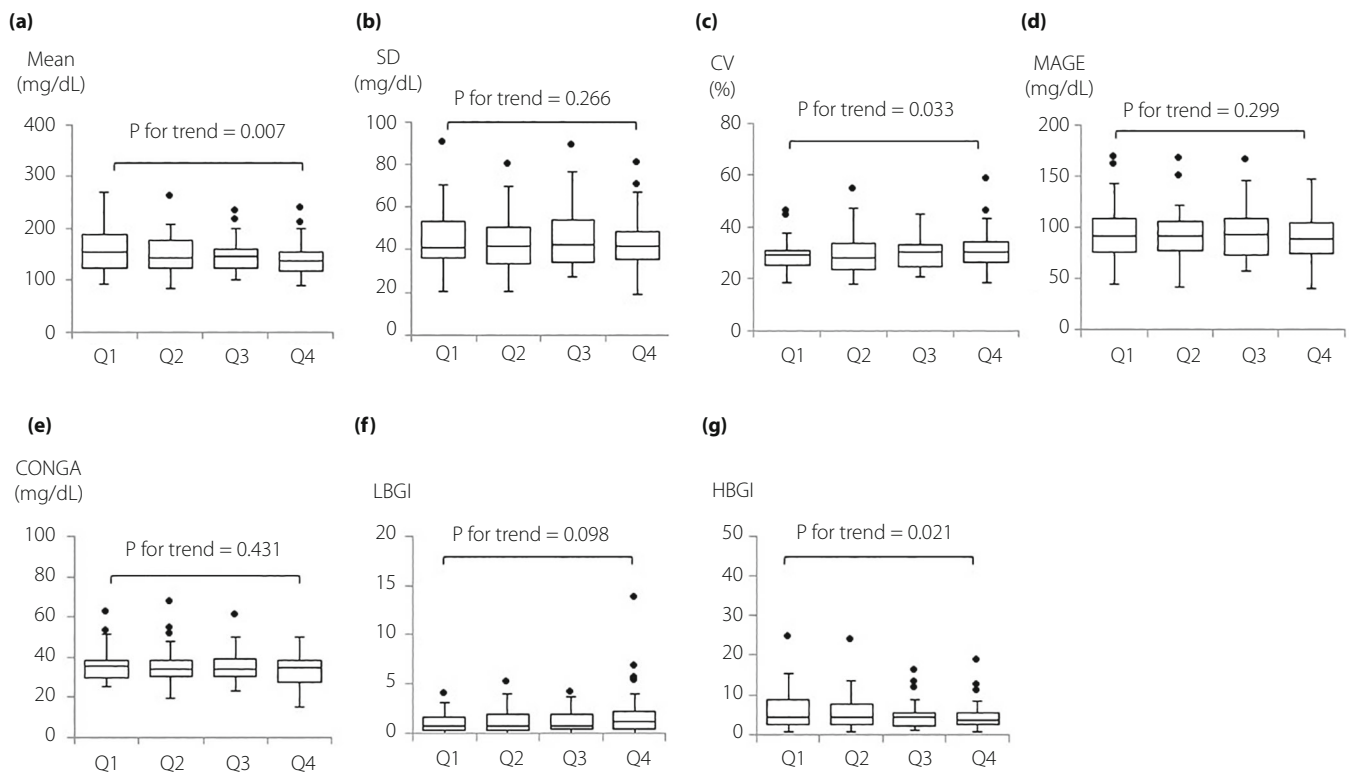

Figure 2 | Association between the low-carbohydrate-diet score and glycemic variability indices derived from continuous glucose monitoring. (a) Mean sensor glucose, (b) standard deviation (SD), (c) coefficient of variation (CV), (d) mean amplitude of glycemic excursion (MAGE), (e) continuous overlapping net glycemic action calculated every 1 h (CONGA-1 h), (f) low blood glucose index (LBGI), and (g) high blood glucose index (HBGI). Data are shown in box and whisker plots using the Tukey method. The black dots are outliers. Q1, quadrant 1; Q2, quadrant 2; Q3, quadrant 3; Q4, quadrant 4.

No significant association was found between the low-carbohydrate-diet score and the use of antihypertensive medication (P for trend = 0.089) and systolic (P for trend = 0.144) or diastolic (P for trend = 0.342) blood pressure.

We subsequently investigated the association between the low-carbohydrate-diet score and vascular complications of type 2 diabetes mellitus. No significant association was noted between the low-carbohydrate-diet score and brachial–ankle
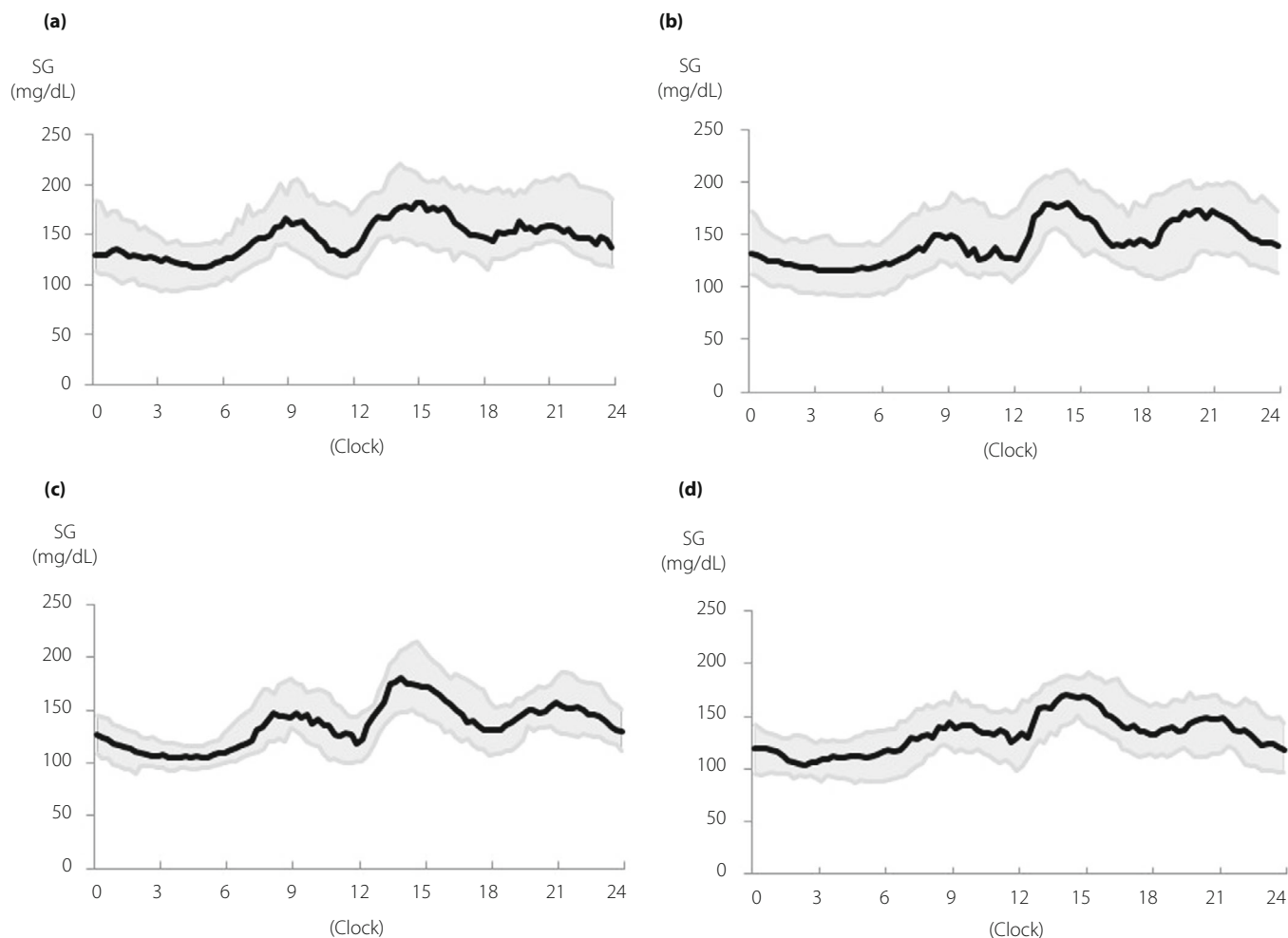
Figure 3 | Median and interquartile range curves drawn from continuous glucose monitoring. The bold line indicates the median. The gray-shaded band indicates the interquartile range. (a) Quadrant 1 (Q1), (b) quadrant 2 (Q2), (c) quadrant 3 (Q3), (d) quadrant 4 (Q4).

Table 3 | Association between the low-carbohydrate-diet score and serum lipids and blood pressure

	Q1 (N = 45)	Q2 (N = 47)	Q3 (N = 44)	Q4 (N = 41)	P for trend
T-chol, mg/dL	177.0 (155.0–201.0)	175.0 (145.5–193.0)	180.5 (159.5–201.8)	180.0 (165.0–207.0)	0.166
HDL-chol, mg/dL	54.0 (41.0–62.0)	52.0 (45.5–69.5)	55.5 (46.5–72.3)	62.0 (53.0–74.0)	0.003
TG, mg/dL	132.0 (101.0–171.0)	123.0 (92.5–150.5)	102.5 (68.3–146.3)	83.0 (69.0–113.0)	<0.001
EPA/AA	0.25 (0.18–0.35)	0.23 (0.17–0.38)	0.33 (0.16–0.40)	0.24 (0.15–0.44)	0.551
DHA/AA	0.61 (0.51–0.81)	0.51 (0.42–0.85)	0.65 (0.50–0.81)	0.55 (0.48–0.71)	0.229
SBP, mmHg	122 (110–137)	129 (118–141)	128 (116–140)	130 (118–141)	0.144
DBP, mmHg	72 (67–81)	76 (70–85)	76 (70–82)	76 (69–81)	0.342
eGFR, mL/min/1.73 m²	70.0 (55.0–82.0)	69.0 (61.5–81.0)	72.0 (63.5–86.5)	71.0 (65.0–83.0)	0.150
UACR, mg/g·Crn	13.9 (6.7–44.7)	13.2 (6.9–23.9)	15.1 (6.5–73.0)	12.8 (6.4–31.4)	0.357
ba-PWV, cm/s	1691.5 (1521.0–1895.8)	1698.0 (1531.5–1910.0)	1694.3 (1566.6–1864.5)	1555.5 (1487.0–1841.3)	0.276
Antilipidemic drugs, N (%)	28 (62.2%)	31 (66.0%)	27 (61.4%)	26 (63.4%)	0.971
Antihypertensive drugs, N (%)	30 (66.7%)	31 (66.0%)	30 (68.2%)	19 (46.3%)	0.089

AA, arachidonic acid; ba-PWV, brachial–ankle pulse wave velocity; DBP, diastolic blood pressure; DHA, dehydroascorbic acid; eGFR, estimated glomerular filtration rate; EPA, eicosapentaenoic acid; HDL-Chol, high-density lipoprotein-cholesterol; SBP, systolic blood pressure; T-Chol, total-cholesterol; TG, triglyceride; UACR, urine albumin to creatinine ratio.

pulse wave velocity (P for trend = 0.276), UACR (P for trend = 0.357), and eGFR (P for trend = 0.150).

DISCUSSION

The results of this study showed that BMI tended to decrease with increasing low-carbohydrate-diet scores. Furthermore, we observed that not only hyperglycemia indices, such as $TAR_{>180}$ and HBGI, but also lipid profiles were significantly inversely associated with increasing low-carbohydrate-diet scores. In contrast, the present study revealed no significant association between the low-carbohydrate-diet score and GV indices, including SD and mean amplitude of glycemic variability, and vascular complications of type 2 diabetes mellitus, including UACR and ba-PWV.

Similar to the present study, Yamakawa et al.[7] investigated nutrient intake using the BDHQ in Japanese patients with type 2 diabetes mellitus and found a positive correlation between CHO/E and HbA1c; in the present study, we also found a positive correlation between CHO/E and HbA1c (data not shown). The P/E and F/E increase as the CHO/E decreases. Therefore, the low-carbohydrate-diet score that assesses not only CHO/E but also P/E and F/E is useful for investigating the energy-producing nutrients to total energy ratio[9]. However, the low-carbohydrate-diet score has the disadvantage of being affected by the dietary habits of the participant population[27,28]. For example, the Japanese population is known to have a higher CHO/E than the European and American populations[29]. Despite having similar low-carbohydrate-diet scores, the Japanese population has a higher CHO/E than the European and American populations[28]. In this study, unlike CHO/E, no significant association was found between low-carbohydrate-diet scores and HbA1c; however, further study may be necessary to investigate the association between the two.

The results of this study indicate that the intake of trace elements, including iron, decreases with increasing low-carbohydrate-diet scores. Since the HbA1c levels are affected by iron metabolism[30], it would be necessary to investigate other glycemic control indices besides HbA1c to evaluate the relationship between CHO/E and glycemic control status. Therefore, we investigated the association between the low-carbohydrate-diet score and continuous glucose monitoring indices and found a significant association between the low-carboydrate-diet score and hyperglycemia indices, such as $TAR_{>180}$ and HBGI. Conversely, the results of this study showed that neither glycemic variability indices, including mean amplitude of glycemic variability and continuous overlapping net glycemic action calculated every 1 h, nor hypoglycemic indices, including $TBR_{<70}$ and LBGI, were significantly associated with CHO/E. It has been reported that CGM-derived glycemic variability indices, including SD and mean amplitude of glycemic variability were significantly improved in low-carbohydrate diets with a carbohydrate intake of <50 g/day compared with high-carbohydrate diets[31]. However, in this study, no cases of a carbohydrate intake of <50 g/day among the participants were noted,

indicating that a moderately carbohydrate-restricted diet may have a limited impact on glycemic variability. In patients with type 2 diabetes mellitus, oscillating glucose levels have been reported to worsen oxidative stress and vascular endothelial more than constant high blood glucose levels[32]. On the other hand, this study showed that the low-carbohydrate-diet score was not associated with glycemic variability indices and vascular complications of type 2 diabetes mellitus. However, a long-term prospective study is needed to clarify the association between a low-carbohydrate diet and diabetes complications.

It has been reported that low-carbohydrate diets significantly decrease triglyceride levels and increase HDL cholesterol levels compared with high-carbohydrate diets in patients with type 2 diabetes mellitus[2]. In this study, there was only one case with a CHO/E of <26%; however, higher low-carbohydrate-diet scores were associated with lower triglycerides and higher HDL levels. Although SFA/E increased with increasing low-carbohydrate-diet scores, MUFA/E and PUFA/E also showed significant increases, suggesting a possible positive effect on lipid metabolism.

Low-carbohydrate diets (CHO/E of <26%) are useful for weight loss in the short-term; however, after 6–12 months, there is no significant difference in the weight loss effect compared with moderate-carbohydrate diets (CHO/E of 26–45%) and high-carbohydrate diets (CHO/E of >45%)[2,4]. While some reports have shown no weight loss effect for moderate-carbohydrate diets, others have shown significant weight loss compared with high-carbohydrate diets[4]. In this study, the median CHO/E of the high low-carbohydrate-diet score group was 43.8%, with the BMI significantly and inversely associated with increased low-carbohydrate-diet scores. These results suggest that carbohydrate restriction of 40–45% may be useful for obese Japanese patients.

Decreased serum zinc levels have been reported to be associated with poor glycemic control[33], and the results of this study indicated that zinc intake decreased as the low-carbohydrate-diet score decreased. Low-carbohydrate-diet scores decrease as CHO/E increases, whereas zinc intake decreases as CHO/E increases[34]. In addition, the energy ratio of each energy-producing nutrient for proper intake of trace elements is reported to be 50–54% for CHO/E, 18–20% for P/E, and 28–30% for F/E[35]. An ROC analysis was performed in this study to determine the best discrimination point between the low-carbohydrate-diet score and adequate zinc intake. As a result, a low-carbohydrate-diet score of 16 points was calculated as the threshold for zinc intake (AUROC = 0.678; sensitivity = 74.4%; specificity = 60.5%; $P < 0.001$). The results of this study revealed that the low-carbohydrate-diet score was associated with zinc intake, whereas carbohydrate quality, but not carbohydrate intake, was associated with trace element intake[36]. The interrelationship between carbohydrate intake, trace element intake, and glycemic control may require further investigation.

This study had some limitations. First, it was a cross-sectional study. Long-term prospective studies on the

relationship between the ratio of energy-producing nutrients to total energy intake and diabetes complications are needed. Second, the low-carbohydrate-diet score is a useful index for evaluating carbohydrate-restricted diets because it is calculated from the ratio of each energy-producing nutrient[9]. However, this score may be influenced by the eating habits of the subject population and is a subject for future study[27,28]. Third, the intensity of the activities of daily living in patients with type 2 diabetes mellitus affects glycemic control. Because this study did not assess the influence of the subjects' lifestyles, further investigation is required. Lastly, while the questionnaire allowed for the objective assessment of energy intake and the ratio of nutrients to total energy intake, there was also the possibility of under-reporting dietary intake. Although the low-carbohydrate-diet score was used to reduce bias because of under-reporting of dietary intake, the assessment of dietary content by the dietitian is warranted for analyzing the detailed relationship of low-carbohydrate diets with glycemic variability.

In conclusion, the results of this study showed that moderate-carbohydrate diets positively impact weight control and lipid metabolism but may have a limited effect on short-term glycemic variability in patients with type 2 diabetes mellitus.

DISCLOSURE
The authors declare that they have no potential conflicts of interest to disclose.

Approval of the research protocol: This study was approved by the Ethics Committee of Hyogo Medical University Hospital (Approval No. 0390).

Informed consent: All participants provided informed consent and signed informed consent forms.

Registry and the registration no. of the study/trial: UMIN000032143.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | The receiver operating characteristic curve for determining the threshold of the low-carbohydrate-diet score for each parameter.

Table S1 | Calculation of the low-carbohydrate-diet score.