BMJ Open Diabetes Research & Care

Association between brain imaging biomarkers and continuous glucose monitoring-derived glycemic control indices in Japanese patients with type 2 diabetes mellitus

Chikako Inoue,[1] Yoshiki Kusunoki ,[1] Mana Ohigashi,[1] Keiko Osugi,[1] Kazuhiro Kitajima,[2] Ayako Takagi,[1] Maki Inoue,[1] Chisako Yagi,[1] Taku Tsunoda,[1] Miki Kakutani,[1] Manabu Kadoya,[1] Kosuke Konishi,[1] Tomoyuki Katsuno,[1] Hidenori Koyama,[1] The Hyogo Diabetes Hypoglycemia Cognition Complications (HDHCC) Study Group

To cite: Inoue C, Kusunoki Y, Ohigashi M, *et al*. Association between brain imaging biomarkers and continuous glucose monitoring-derived glycemic control indices in Japanese patients with type 2 diabetes mellitus. *BMJ Open Diab Res Care* 2024;**12**:e003744. doi:10.1136/bmjdrc-2023-003744

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjdrc-2023-003744).

Received 1 September 2023
Accepted 19 December 2023

For numbered affiliations see end of article.

Correspondence to
Dr Yoshiki Kusunoki;
ykusu@hyo-med.ac.jp

ABSTRACT

Introduction Although type 2 diabetes mellitus (T2DM) is associated with alterations in brain structure, the relationship between glycemic control indices and brain imaging markers remains unclear. This study aimed to investigate the association between continuous glucose monitoring (CGM)-derived glycemic control indices and brain imaging biomarkers assessed by MRI.

Research design and methods This cross-sectional study included 150 patients with T2DM. The severity of cerebral white matter lesions (WMLs) was assessed using MRI for deep and subcortical white matter and periventricular hyperintensities. The degree of medial temporal lobe atrophy (MTA) was assessed using voxel-based morphometry. Each participant wore a retrospective CGM for 14 consecutive days, and glycemic control indices, such as time in range (TIR) and glycemia risk index (GRI), were calculated.

Results The proportion of patients with severe WMLs showed a decreasing trend with increasing TIR (*P* for trend=0.006). The proportion of patients with severe WMLs showed an increasing trend with worsening GRI (*P* for trend=0.011). In contrast, no significant association was observed between the degree of MTA and CGM-derived glycemic control indices, including TIR (*P* for trend=0.325) and GRI (*P* for trend=0.447).

Conclusions The findings of this study indicate that the severity of WMLs is associated with TIR and GRI, which are indices of the quality of glycemic control.

Trial registration number UMIN000032143.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Epidemiological studies have reported that type 2 diabetes mellitus is associated with alterations in brain structure.

⇒ The association between brain imaging biomarkers and continuous glucose monitoring (CGM)-derived glycemic control indices remains unclear.

WHAT THIS STUDY ADDS

⇒ The severity of cerebral white matter lesions (WMLs) is associated with CGM-derived glycemic control indices, such as time in range and glycemia risk index.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings indicate that CGM-derived indices are useful glycemic control indicators for the prevention of severe WMLs.

INTRODUCTION

The number of cases and the prevalence of type 2 diabetes mellitus (T2DM) have continuously increased in recent years.[1] Furthermore, many epidemiological studies have reported that T2DM is associated with an increased risk of cognitive impairment and dementia.[2–4] Several studies have sought to determine whether T2DM is associated with specific brain changes.[5] For example, global brain atrophy, medial temporal lobe atrophy (MTA), and cerebral white matter lesions (WMLs) are brain imaging biomarkers that can assess parenchymal brain injury.[5] Reduced hippocampus and amygdala volumes have been found in studies using MRI in patients with T2DM compared with those without T2DM.[6] On the other hand, some reports indicate that hippocampal atrophy is not prominent in patients with T2DM, but rather a reduction in global brain volume.[7] In addition, WML, a form of cerebral small vessel disease (CSVD), has been linked to an increased risk of stroke, all-cause mortality, and dementia,[8–11] and T2DM has been reported to be associated with the progression of WMLs.[12]

Regarding the association between brain imaging markers and glycemic control indices, a significant association between increased 2-hour blood glucose levels in the 75 g oral glucose tolerance test and gray matter atrophy in various brain regions has been reported.[13] While some studies found a significant association between high Hemoglobin A1c (HbA1c) levels and WMLs,[14] others found no significant association.[15 16] Although HbA1c is often used as a glycemic control indicator, it limitedly measures average blood glucose levels, and thus fails to adequately assess hypoglycemia or postprandial hyperglycemia.[17]

Advances in continuous glucose monitoring (CGM) leading to its increasing use in daily clinical practice. CGM can provide detailed information on glycemic control, including postprandial hyperglycemia and nocturnal hypoglycemia. Measuring HbA1c, glycated albumin (GA), and CGM-derived glycemic control indices, simultaneously, may provide implications for examining the association between glycemic control status and brain imaging biomarkers in patients with T2DM. This study aimed to investigate the association of WMLs and MTA as assessed by MRI with CGM-derived glycemic control indices in Japanese patients with T2DM.

METHODS

Study design and participants

This study was conducted as part of the Hyogo Diabetes Hypoglycemia Cognition Complications (HDHCC) study. The HDHCC study is a multicenter cohort study designed to investigate the relationship between glycemic control and chronic diabetes complications, such as cognitive impairment in outpatient clinic patients. This study included patients with T2DM aged 50–79 years who underwent retrospective CGM and MRI scans at Hyogo Medical University Hospital (Japan) between April 2018 and October 2022. The exclusion criteria were as follows: (1) participants with dementia, (2) those with severe hepatic dysfunction (defined as alanine transaminase ≥threefold the upper limit of normal), (3) those with chronic renal failure (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2), (4) those unable to obtain CGM data for >7 consecutive days, (5) those with type 1 diabetes, and (6) those deemed ineligible for this study by their physician.

Assessment of the glycemic control indices

The FreeStyle Libre Pro system (Abbott Japan, Tokyo, Japan) was used as a retrospective CGM, and interstitial glucose levels were monitored for 14 consecutive days. A mean absolute relative difference (MARD) of 11.4% has been reported for this CGM system after 14 days of use.[18] The measurement accuracy of the FreeStyle Libre Pro system has been reported to decrease slightly on days 1 and 14 of use, with MARDs of 11.9%, 10.9%, and 10.8% on days 2, 7, and 14, respectively.[18] An international consensus statement on the use of CGM metrics in clinical trials recommends that all CGM data should be used for analysis regardless of the accuracy of CGM measurement in conducting clinical studies[17]; however, in this study, the results using glucose data for 10 days from day 3 to day 12 of CGM use are also included, considering the measurement accuracy of the FreeStyle Libre Pro system.

Glycemic control indices were calculated using methods described previously.[17 19–22] The following glycemic control indices were calculated: (1) mean sensor glucose (SG), (2) coefficient of variation (CV), (3) time spent with SG values in the range of 70–180 mg/dL (time in range (TIR)), (4) time spent with SG values higher than 250 mg/dL (time above range ($TAR^{>250}$)), (5) time spent with SG values higher than 180 mg/dL ($TAR^{>180}$), (6) time spent with SG values below 70 mg/dL (time below range ($TBR^{<70}$)), (7) time spent with SG values below 54 mg/dL ($TBR^{<54}$), (8) glycemia risk index (GRI), (9) hyperglycemia component (HyperCompo) in GRI calculation, (10) hypoglycemia component (HypoCompo) in GRI calculation, (11) high blood glucose index (HBGI), and (12) low blood glucose index (LBGI). HbA1c and GA were measured while the CGM device was worn.

HbA1c, GA, eGFR, and urine albumin-to-creatinine ratio were determined at the time of attaching the CGM device.

Assessment of brain imaging biomarkers

All participants underwent MRI with a 3.0-T scanner (Achieva 3.0T MR system, Koninklijke Philips N.V., Amsterdam, Netherlands). The axial T2-weighted images were acquired using a turbo spin echo technique with 4 mm slices and a 1.5 mm interslice gap (repetition time (TR), 3000 ms; echo time (TE), 80 ms).

Periventricular hyperintensity (PVH), and deep and subcortical white matter hyperintensity (DSWMH) were considered as WMLs. WMLs were assessed by a radiologist (Department of Radiology, School of Medicine, Hyogo Medical University, Japan) who was blinded to the patient's background and glycemic control status. The same radiologist evaluated all images to avoid discrepancies in the image reading results. WMLs were assessed in accordance with the Brain Doc guidelines 2019, and lesions corresponding to grade 3 on the Fazekas scale for PVH and DSWMH were regarded as severe cases of WMLs[23 24]

The MTA was assessed using VSRAD advanced software (Eisai, Tokyo, Japan). Three-dimensional sagittal sections of T1-weighted images with 1 mm slices and no interslice gap were obtained for VSRAD using a fast field echo technique (TR, 7.46 ms; TE, 3.41 ms). VSRAD quantitatively evaluates the degree of brain atrophy in the volume of interest (VOI, which includes the participant's entorhinal cortex, amygdala, and hippocampus) as a Z-score by statistically comparing it with a brain MRI database of cognitively normal participants. Assessing MTA severity using VSRAD is effectively used for determining early

Alzheimer's disease.[25 26] Here, Z-scores in the target VOI of≥1.0 were characterized as MTA.

Other parameters

Information regarding the duration of T2DM and comorbidities was obtained from the attending physician or the patient's medical records. We defined dyslipidemia as the presence of low-density lipoprotein cholesterol level of ≥140 mg/dL, triglyceride level of ≥150 mg/dL, high-density lipoprotein cholesterol level of ≤40 mg/dL, or dyslipidemia treatment. Hypertension was defined as systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mmHg, or hypertension treatment.

Statistical analysis

The results are presented as medians (IQRs) unless otherwise stated. Participants of this study were divided into three groups for HbA1c (<7.0% (52 mmol/mol), 7.0%–7.9% (52–62 mmol/mol), and ≥8.0% (63 mmol/mol)), TIR (<50.0%, 50.0%–70.0%, and >70.0%), $TAR^{>250}$ (<5.0%, 5.0%–10.0%, and >10.0%), $TAR^{>180}$ (<25.0%, 25.0%–50.0%, and >50.0%), $TBR^{<70}$ (<1.0%, 1.0%–4.0%, and >4.0%), HyperCompo (<15%, 15%–30%, and >30%), HypoCompo (<1.0%, 1.0%–2.4%, and >2.4%), and HBGI (<4.5, 4.5–9.0, and >9.0).[17 22 27] The observed values among participants were also divided into two groups for $TBR^{<54}$ (<1.0% and ≥1.0%) and LBGI (<2.5 and ≥2.5).[17 27] Patients with type 1 diabetes with CVs of >36% are at a higher risk of hypoglycemia,[17 28] whereas patients with T2DM with CVs of <30% avoid hypoglycemia.[29] Therefore, in this study, patients were categorized into two groups based on their CV value: <30.0% and ≥30.0%. Furthermore, the participants were divided into four groups based on their GA/HbA1c and GRI values.

The Jonckheere-Terpstra test was used to compare the data trends among the three groups. The Cochran-Armitage test was used to determine the ratio trends between the three groups. The Mann-Whitney U test was used to compare continuous variables, and the χ^2 test, or Fisher's exact test was used to compare categorical data.

Univariate logistic regression analysis was performed with the severity of WMLs as the objective variable and each glycemic control index as the explanatory variable. The progression of WMLs has been reported to be strongly associated with aging, hypertension, and dyslipidemia.[8–10] Therefore, a multivariate logistic regression analysis with the severity of WMLs as the objective variable and each glycemic control index and age as explanatory variables was performed using Model 1. Furthermore, a multivariate logistic regression analysis was performed using Model 2, a model that added the presence of hypertension and dyslipidemia as an explanatory variable to Model 1, and Model 3, a model that added a history of cerebrovascular disease as an explanatory variable to Model 2.

A simple linear regression analysis was performed with the Z-score in the VOI as the objective variable and each glycemic control index as the explanatory variable. Next, multiple regression analysis was performed with the Z-score in the VOI as the objective variable and each glycemic control index and age as explanatory variables (Model 1). Furthermore, multiple regression analysis was performed using Model 2, which added the presence of hypertension and dyslipidemia, history of cerebrovascular disease, sex, body mass index (BMI), and smoking as explanatory variables to Model 1.

In this study, a p value of <0.05 was considered statistically significant. Statistical analyses were conducted using the BellCurve software V.4.04 (Social Survey Research Information, Tokyo, Japan).

RESULTS

Study participants

The characteristics of the participants are shown in online supplemental table 1. There were 150 participants, comprising 44 women and 106 men. The age was 69.0 (64.0–72.0) years; the duration of T2DM was 14.0 (8.0–24.0) years; BMI was 24.0 (22.3–26.0) kg/m^2; HbA1c was 7.0 (6.6–7.6)% (52 (48–59) mmol/mol); GA was 18.3 (16.3–20.4)%; GA/HbA1c was 2.6 (2.4–2.8). For the CGM index, the value analyzed using all sensor data for the mean SG value was 141.9 (125.1–165.8) mg/dL, and the value analyzed excluding certain days was 141.0 (124.2–165.7) mg/dL. TIR calculated from all CGM data was 77.9 (65.3–88.1) mg/dL, $TAR^{>250}$ was 1.1% (0%–6.7%), $TAR^{>180}$ was 18.1% (8.4%–34.0%), $TBR^{<70}$ was 0.2% (0%–2.1%), $TBR^{<54}$ was 0% (0%–0%), and GRI was 22.1% (12.6%–40.9%).

Forty-nine (32.7%) participants had severe deep subcortical WMLs (DSWMLs) and 23 (15.3%) participants had severe periventricular WMLs (PWMLs). All participants with severe PWMLs also had severe DSWMLs. The Z-score in the target VOI assessed using voxel-based morphometry (VBM) for the participants of this study was 0.58 (0.43–0.83). Twenty (13.3%) participants had a Z-score of ≥1.0, indicating MTA.

Relationship between WMLs and glycemic control indices

Table 1 and online supplemental table 2 show the differences in clinical parameters of participants with and without severe WMLs. Participants with severe WMLs had higher rates of prior cerebrovascular disease than those without severe WMLs. Although there were no significant differences in age, sex, duration of diabetes, HbA1c, or smoking status between the two groups, the group with severe WMLs had significantly more patients with hypertension (p=0.024) and a history of cerebrovascular disease (p=0.003). In contrast, the group with severe WMLs had significantly fewer patients with dyslipidemia (p=0.041). In addition, patients with severe WMLs had lower mini-mental state examination (MMSE) scores. No significant differences were found in the use of diabetes medications between the two groups.

The relationship between WMLs and CGM-derived glycemic control indices is shown in figure 1. The

Table 1 Differences in clinical parameters according to the presence or absence of severe cerebral white matter lesions (WMLs) and medial temporal atrophy (MTA)

	Without severe WMLs (N=101)	With severe WMLs (N=49)	P value	Without MTA (N=130)	With MTA (N=20)	P value
Age (years old)	68.0 (63.0–72.0)	70.0 (65.0–73.0)	0.112	68.0 (63.0–72.0)	72.0 (70.8–73.0)	<0.001
Male (%)	73.3	65.3	0.416	68.5	85.0	0.102
BMI (kg/m^2)	24.0 (22.5–26.3)	23.6 (21.8–25.3)	0.385	24.0 (22.5–26.0)	23.0 (21.7–27.7)	0.372
Disease duration (years)	13.0 (6.0–22.0)	17.0 (10.0–25.0)	0.125	12.5 (7.0–21.8)	26.0 (16.0–32.3)	<0.001
HbA1c (%)	7.0 (6.6–7.6)	7.1 (6.5–7.5)	0.784	7.1 (6.6–7.6)	6.9 (6.5–7.3)	0.514
GA/HbA1c	2.6 (2.4–2.7)	2.6 (2.4–2.9)	0.267	2.6 (2.4–2.7)	2.8 (2.6–3.0)	0.003
SBP (mm Hg)	126.0 (114.0–135.0)	128.0 (116.0–139.0)	0.235	126.5 (116.0–136.0)	131.0 (117.5–140.8)	0.351
DBP (mm Hg)	76.0 (69.0–81.0)	75.0 (69.0–82.0)	0.735	76.0 (70.0–82.0)	68.5 (66.0–78.3)	0.053
Non-HDL (mg/dL)	119.0 (101.0–140.0)	125.0 (98.0–147.0)	0.646	122.0 (101.3–146.0)	121.0 (90.8–143.0)	0.575
HDL (mg/dL)	55.0 (45.0–66.0)	55.0 (50.0–66.0)	0.488	55.5 (46.0–66.0)	53.0 (49.5–71.5)	0.890
eGFR (mL/min/1.73 m^2)	72.0 (65.0–82.0)	70.0 (52.0–82.0)	0.143	72.0 (62.5–82.0)	63.0 (47.0–73.8)	0.032
History of IHD (%)	10.9	18.4	0.314	13.1	15.0	0.732
History of CVD (%)	5.0	22.4	0.003	9.2	20.0	0.232
Current smoker (%)	20.8	22.4	0.984	20.8	25.0	1.000
Dyslipidemia (%)	85.1	69.4	0.041	83.8	55.0	0.006
Hypertension (%)	59.4	79.6	0.024	63.8	80.0	0.207
MMSE	30.0 (29.0–30.0)	29.0 (28.0–30.0)	0.007	30.0 (29.0–30.0)	29.0 (28.0–30.0)	0.389
Metformin (%)	50.5	40.8	0.348	49.2	35.0	0.111
SU/Glinides (%)	26.7	20.4	0.522	24.4	30.4	0.800
DPP-4 is (%)	44.6	51.0	0.569	46.9	45.0	0.500
SGLT2 is (%)	18.8	34.7	0.053	23.1	30.0	0.794
TZDs and/or α-GIs (%)	19.8	10.2	0.166	16.5	17.4	1.000
Insulin (%)	23.8	34.7	0.225	25.4	40.0	0.447
GLP-1 RAs (%)	13.9	14.3	1.000	13.8	15.0	1.000
TIR (%)	79.3 (68.9–88.1)	71.2 (45.7–86.8)	0.029	78.0 (65.2–87.8)	74.5 (65.6–90.8)	0.853
GRI (%)	20.9 (12.5–32.7)	35.2 (13.1–61.1)	0.014	21.9 (12.9–40.8)	24.1 (8.8–44.2)	0.941

The results are the median values (IQR) or percentages. The Mann-Whitney U test was used to compare continuous variables, and the χ^2 test or Fisher's exact test was used to compare categorical data.

BMI, body mass index; CV, coefficient of variation; CVD, cerebrovascular disease; DBP, diastolic blood pressure; DPP-4 i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GA, glycated albumin; GLP-1 RA, glucagon-like peptide-1 receptor agonist; GRI, glycemia risk index; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HyperCompo, hyperglycemia component; HypoCompo, hypoglycemia component; IHD, ischemic heart disease; LBGI, low blood glucose index; MMSE, mini-mental state examination; SBP, systolic blood pressure; SG, sensor glucose; SGLT2 i, sodium-glucose transporter 2 inhibitor; SU, sulfonylurea; TAR, time above range; TBR, time below range; TIR, time in range; α-GI, alpha-glucosidase inhibitor.

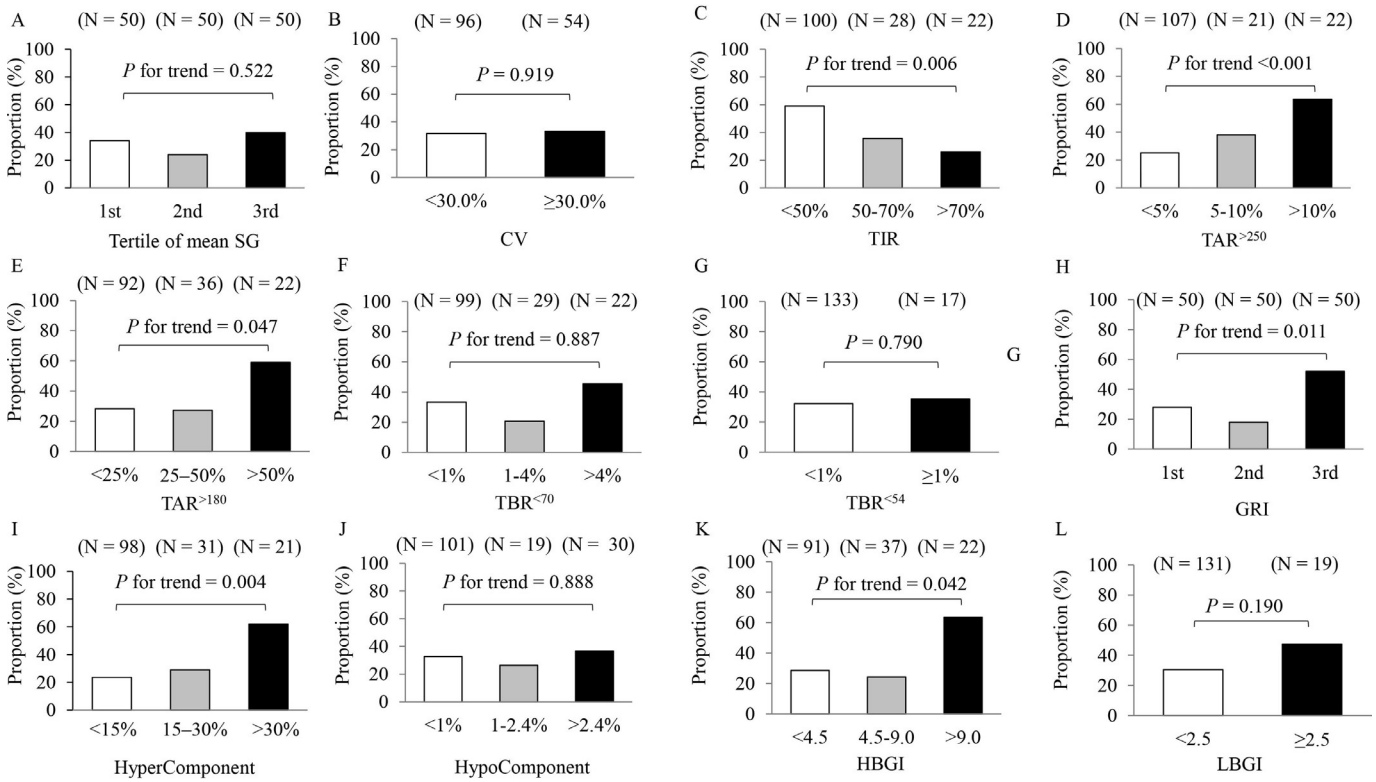

Figure 1 Comparisons of the prevalence of severe cerebral white matter lesions (WMLs) based on glycemic control indices. (A) Mean sensor glucose (SG), (B) coefficient of variation (CV), (C) time spent with SG values in the range of 70–180 mg/dL (time in range (TIR)), (D) time spent with SG values higher than 250 mg/dL (time above range ($TAR^{>250}$)), (E) time spent with SG values higher than 180 mg/dL ($TAR^{>180}$), (F) time spent SG values below 70 mg/dL (time below range ($TBR^{<70}$)), (G) time spent SG values below 54 mg/dL ($TBR^{<54}$), (H) glycemia risk index (GRI), (I) hyperglycemia component (HyperCompo), (J) hypoglycemia component (HypoCompo), (K) high blood glucose index (HBGI), and (L) low blood glucose index (LBGI). The prevalence of severe WML was examined using the Cochran-Armitage test.

proportion of patients with severe WMLs decreased with increasing TIR (*P* for trend=0.006). On the other hand, the proportion of patients with severe WMLs increased with increase in median values of hyperglycemic indices, such as $TAR^{>250}$ (*P* for trend<0.001), $TAR^{>180}$ (*P* for trend=0.047), HyperCompo (p=0.004), and HBGI (p=0.042). Similarly, the proportion of patients with severe cerebral WMLs increased with increasing GRI (p=0.011).

The association between cerebral WMLs and hypoglycemic indices was then investigated. No significant association was observed between $TBR^{<70}$ (*P* for trend=0.887) or $TBR^{<54}$ (p=0.790) and the proportion of patients with severe WMLs. Furthermore, no significant association was found between the proportion of patients with severe cerebral WMLs and HypoCompo (*P* for trend=0.888) and LBGI (p=0.190).

Next, univariate logistic regression analysis was performed with WML severity as the objective variable and each glycemic control index as an explanatory variable (table 2 and online supplemental table 3). The results showed that the WML severity was significantly associated with TIR calculated from all CGM data (crude OR, 0.976; 95% CI, 0.959–0.993; p=0.006), $TAR^{>250}$ (crude OR, 1.063; 95% CI, 1.020 to 1.108; p=0.004), $TAR^{>180}$ (crude OR, 1.018; 95% CI, 1.002 to 1.035; p=0.031), GRI (crude OR, 1.026; 95% CI, 1.011 to 1.041; p<0.001), HyperCompo (crude OR, 1.019; 95% CI, 1.004 to 1.035; p=0.012), and HBGI (crude OR, 1.127; 95% CI, 1.031 to 1.232; p=0.009). In contrast, no significant association was found between severe WMLs and HbA1c (crude OR, 1.155; 95% CI, 0.754 to 1.768; p=0.508), mean SG (crude OR, 1.010; 95% CI, 0.999 to 1.020; p=0.063), or CV (crude OR, 1.022; 95% CI, 0.967 to 1.080; p=0.436). Furthermore, no significant associations were found between WLM severity and hypoglycemic indices, such as $TBR^{<54}$ (crude OR, 1.125; 95% CI, 0.934 to 1.354; p=0.214), HypoCompo (crude OR, 1.016; 95% CI, 0.994 to 1.038; p=0.146), and LBGI (crude OR, 1.104; 95% CI, 0.894 to 1.363; p=0.359). Similar results were obtained for the glycemic control indices calculated from CGM data with specific days removed.

For Model 1, we performed a multivariate logistic regression analysis with severe WMLs as the objective variable and each glycemic control index (calculated from all CGM data) and age as explanatory variables. The results indicated that the severity of WMLs was significantly associated with TIR (OR, 0.976; 95% CI, 0.958 to 0.993, p=0.007), $TAR^{>250}$ (OR, 1.060; 95% CI, 1.017 to 1.106, p=0.006), $TAR^{>180}$ (OR, 1.020; 95% CI, 1.002 to 1.040, p=0.034), GRI (OR, 1.026; 95% CI,

Table 2 Association between the severity of cerebral white matter lesions and glycemic control indices

	Severe white matter lesions				
	OR (95% CI)	P value		OR (95% CI)	P value
HbA1c			GA/HbA1c		
Univariate	1.155 (0.754 to 1.768)	0.508	Univariate	2.338 (0.896 to 6.102)	0.083
Model 1	1.163 (0.794 to 2.132)	0.494	Model 1	2.013 (0.750 to 5.406)	0.165
Model 2	1.335 (0.838 to 2.126)	0.225	Model 2	1.513 (0.519 to 4.408)	0.448
Model 3	1.326 (0.820 to 2.145)	0.250	Model 3	1.045 (0.331 to 3.296)	0.940
Mean SG			CV		
Univariate	1.010 (0.999 to 1.020)	0.063	Univariate	1.022 (0.967 to 1.080)	0.436
Model 1	1.009 (0.999 to 1.020)	0.091	Model 1	1.024 (0.969 to 1.083)	0.403
Model 2	1.011 (1.000 to 1.022)	0.048	Model 2	1.017 (0.960 to 1.079)	0.562
Model 3	1.011 (1.000 to 1.022)	0.051	Model 3	1.015 (0.956 to 1.077)	0.628
TIR			$TAR^{>250}$		
Univariate	0.976 (0.959 to 0.993)	0.006	Univariate	1.063 (1.020 to 1.108)	0.004
Model 1	0.976 (0.958 to 0.993)	0.007	Model 1	1.060 (1.017 to 1.106)	0.006
Model 2	0.973 (0.955 to 0.991)	0.004	Model 2	1.069 (1.024 to 1.116)	0.003
Model 3	0.973 (0.955 to 0.992)	0.005	Model 3	1.066 (1.021 to 1.112)	0.003
$TAR^{>180}$			$TBR^{<70}$		
Univariate	1.018 (1.002 to 1.035)	0.031	Univariate	1.041 (0.987 to 1.098)	0.137
Model 1	1.020 (1.002 to 1.040)	0.034	Model 1	1.049 (0.992 to 1.110)	0.093
Model 2	1.021 (1.003 to 1.039)	0.022	Model 2	1.045 (0.984 to 1.110)	0.151
Model 3	1.021 (1.003 to 1.039)	0.022	Model 3	1.047 (0.982 to 1.115)	0.159
$TBR^{<54}$			GRI		
Univariate	1.125 (0.934 to 1.354)	0.214	Univariate	1.026 (1.011 to 1.041)	<0.001
Model 1	1.148 (0.952 to 1.384)	0.149	Model 1	1.026 (1.011 to 1.042)	<0.001
Model 2	1.150 (0.945 to 1.399)	0.164	Model 2	1.029 (1.012 to 1.046)	<0.001
Model 3	1.145 (0.932 to 1.405)	0.197	Model 3	1.029 (1.012 to 1.046)	<0.001
HyperCompo			HypoCompo		
Univariate	1.019 (1.004 to 1.035)	0.012	Univariate	1.016 (0.994 to 1.038)	0.146
Model 1	1.019 (1.003 to 1.034)	0.018	Model 1	1.019 (0.997 to 1.042)	0.094
Model 2	1.022 (1.006 to 1.038)	0.008	Model 2	1.018 (0.994 to 1.042)	0.147
Model 3	1.021 (1.005 to 1.038)	0.009	Model 3	1.018 (0.993 to 1.044)	0.154
HBGI			LBGI		
Univariate	1.127 (1.031 to 1.232)	0.009	Univariate	1.104 (0.894 to 1.363)	0.359
Model 1	1.124 (1.026 to 1.232)	0.012	Model 1	1.138 (0.918 to 1.412)	0.238
Model 2	1.142 (1.039 to 1.256)	0.006	Model 2	1.135 (0.903 to 1.426)	0.278
Model 3	1.141 (1.038 to 1.255)	0.006	Model 3	1.127 (0.888 to 1.431)	0.324

Univariate logistic regression analysis was performed with the presence of severe cerebral white matter lesions as the objective variable and each glycemic control index as an explanatory variable. Multivariate logistic regression analysis was then performed on each glycemic control index plus age as explanatory variables in Model 1. Model 2 is Model 1 with the presence of hypertension and dyslipidemia added as explanatory variables, and Model 3 is Model 2 with a history of cerebrovascular disease added as an explanatory variable.
CV, coefficient of variation; GA, glycated albumin; GRI, glycemia risk index; HbA1c, hemoglobin A1c; HBGI, high blood glucose index; HyperCompo, hyperglycemia component; HypoCompo, hypoglycemia component; LBGI, low blood glucose index; SG, sensor glucose; TAR, time above range; TBR, time below range; TIR, time in range.

1.011 to 1.042, p<0.001), HyperCompo (OR, 1.019; 95% CI, 1.003 to 1.034, p=0.018), and HBGI (OR, 1.124; 95% CI, 1.026 to 1.232, p=0.012). In contrast, no significant associations were found between severe WMLs and HbA1c, CV, or hypoglycemic indices, such as $TBR^{<54}$, and LBGI. Similar results regarding the association between severe WMLs and each glycemic control index were obtained in Model 2, in which the presence of hypertension and dyslipidemia were

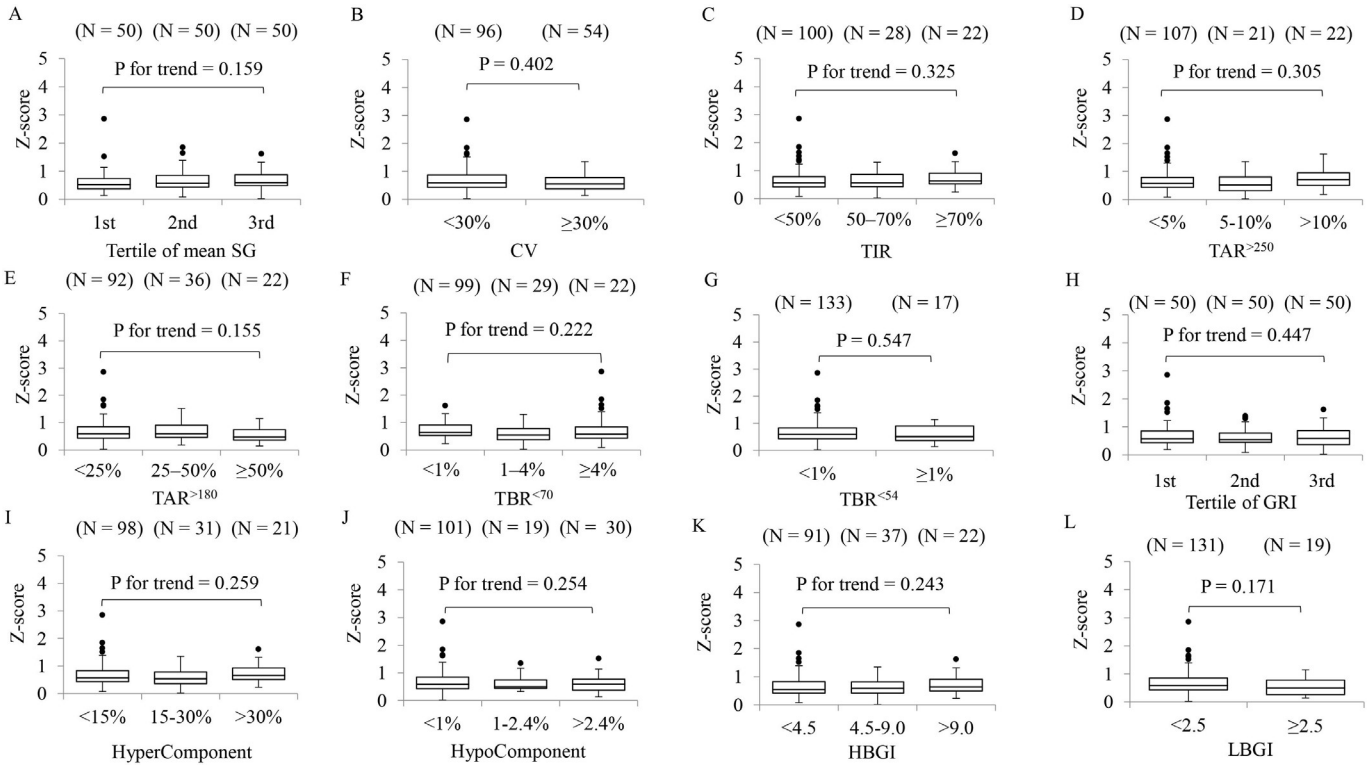

Figure 2 Comparisons of Z-scores in the volume of interest (VOI) based on glycemic control indices. (A) Mean sensor glucose (SG), (B) coefficient of variation (CV), (C) time spent with SG values in the range of 70–180 mg/dL (time in range (TIR)), (D) time spent with SG values higher than 250 mg/dL (time above range ($TAR^{>250}$)), (E) time spent with SG values higher than 180 mg/dL ($TAR^{>180}$), (F) time spent SG values below 70 mg/dL (time below range ($TBR^{<70}$)), (G) time spent SG values below 54 mg/dL ($TBR^{<54}$), (H) glycemia risk index (GRI), (I) hyperglycemia component (HyperCompo), (J) hypoglycemia component (HypoCompo), (K) high blood glucose index (HBGI), and (L) low blood glucose index (LBGI). The Z-scores in the target VOI were examined using the Jonckheere-Terpstra test or the Mann-Whitney U test.

added as covariates, and in Model 3, in which a history of cerebrovascular disease was added as a covariate.

Relationship between brain atrophy and glycemic control indices

Table 1 and online supplemental table 2 show the differences in clinical parameters between subjects with and without MTA. Participants with MTA showed significantly higher age and longer duration of T2DM than those without MTA. The relationship between MTA severity and glycemic control indices is shown in figure 2. There were no significant associations between the presence of MTA and blood glucose control indices, such as HbA1c (*P* for trend=0.381), TIR (*P* for trend=0.325), $TAR^{>180}$ (*P* for trend=0.155), $TBR^{<70}$ (*P* for trend=0.222), or GRI (*P* for trend=0.447).

A simple linear regression analysis was then performed with the Z-score in the VOI as the objective variable and each glycemic control index as the explanatory variable (table 3 and online supplemental table 4). The results showed no significant association between the Z-score in the VOI and any of the CGM-derived glycemic control indices. In contrast, a significant association was observed between the Z-score in the VOI and GA/HbA1c (standardized partial regression coefficient (β) = 0.270, p<0.001). A significant association between the Z-score in the VOI and GA/HbA1c was also found in multivariate-adjusted Model 1 (β=0.210, p=0.009) and Model 2 (β=0.190, p=0.030).

DISCUSSION

The findings of this study show that in Japanese patients with T2DM, the frequency of patients with severe WMLs tends to increase with worsening TIR and GRI, which are indices reflecting the quality of glycemic control. In particular, our results show that the severity of WMLs is associated with hyperglycemia indices, such as TAR, HyperCompo, and HBGI, but not with hypoglycemia indices, such as TBR, HypoCompo, and LBGI. In addition, MTA assessed using VBM was not associated with CGM-derived TIR, TAR, or GRI.

T2DM is associated with an increased risk of dementia, including Alzheimer's disease.[2–4] MTA is a useful indicator of early Alzheimer's disease,[6 25] and T2DM is associated with MTA regardless of vascular pathology.[6 30] On the other hand, some reports indicate that global brain volume reduction rather than MTA is prominent in patients with T2DM.[7] Furthermore, some patients with T2DM who are clinically diagnosed with Alzheimer's disease have diffuse cortical atrophy and less severe MTA.[31 32] The results of this study indicate that MTA and short-term glycemic control indices are not significantly associated in patients with T2DM. However, the number of cases with MTA among the participants was

Table 3 Relationship between medial temporal atrophy and glycemic control index

	Z-scores in the target VOI				
	β	P value		β	P value
HbA1c			GA/HbA1c		
Univariate	−0.002	0.979	Univariate	0.270	<0.001
Model 1	0.004	0.964	Model 1	0.210	0.009
Model 2	0.053	0.506	Model 2	0.190	0.030
Mean SG			CV		
Univariate	0.075	0.364	Univariate	−0.065	0.429
Model 1	0.042	0.594	Model 1	−0.060	0.441
Model 2	0.071	0.371	Model 2	−0.068	0.424
TIR			$TAR^{>250}$		
Univariate	−0.032	0.699	Univariate	0.141	0.085
Model 1	−0.022	0.775	Model 1	0.103	0.192
Model 2	−0.055	0.489	Model 2	0.124	0.117
$TAR^{>180}$			$TBR^{<70}$		
Univariate	0.042	0.613	Univariate	−0.037	0.650
Model 1	0.024	0.763	Model 1	−0.010	0.925
Model 2	0.056	0.476	Model 2	−0.015	0.845
$TBR^{<54}$			GRI		
Univariate	0.023	0.778	Univariate	0.042	0.610
Model 1	0.050	0.525	Model 1	0.040	0.610
Model 2	0.040	0.610	Model 2	0.069	0.389
HyperCompo			HypoCompo		
Univariate	0.076	0.353	Univariate	−0.034	0.683
Model 1	0.051	0.519	Model 1	−0.004	0.964
Model 2	0.081	0.307	Model 2	−0.012	0.883
HBGI			LBGI		
Univariate	0.073	0.376	Univariate	−0.066	0.419
Model 1	0.048	0.546	Model 1	−0.030	0.705
Model 2	0.075	0.341	Model 2	−0.032	0.681

A simple linear regression analysis was performed with the Z-score in the volume of interest (VOI) as the objective variable and each glycemic control index as the explanatory variable. A multiple regression analysis was then performed on each glycemic control index plus age as explanatory variables in Model 1. Furthermore, in Model 2, a multiple regression analysis was performed by adding sex, body mass index, presence of hypertension and dyslipidemia, history of cerebrovascular disease, and smoking as explanatory variables to Model 1.
CV, coefficient of variation; GA, glycated albumin; GRI, glycemia risk index; HbA1c, hemoglobin A1c; HBGI, high blood glucose index; HyperCompo, hyperglycemia component; HypoCompo, hypoglycemia component; LBGI, low blood glucose index; SG, sensor glucose; TAR, time above range; TBR, time below range; TIR, time in range; β, standardized partial regression coefficient.

small as patients with cognitive impairment were excluded from this study, making for a small sample size. In addition, fluctuations in blood glucose concentrations and related osmotic changes may affect brain volumes in patients with T2DM.[5 33] Therefore, larger prospective studies are needed to investigate the association between MTA and CGM-derived glycemic control indices.

Severe WMLs have been linked to an increased risk of stroke, all-cause mortality, and dementia.[8–11] In fact, patients with severe WMLs had significantly lower MMSE scores than those without severe WMLs in this study, which excluded patients with dementia. The main etiology of cerebral WMLs is ischemia, and small arteries penetrating the cerebral white matter are predisposed to atherosclerosis.[9 34] Therefore, risk factors for atherosclerotic diseases, such as hypertension, dyslipidemia, and T2DM, are risk factors for WMLs and stroke.[8–10]

Although many of the subjects in the present study maintained good glycemic control as evidenced by a median HbA1c of 7.0%, the severity of cerebral WMLs was associated with CGM-derived glycemic control indices. Vascular endothelial dysfunction plays a vital role in the progression of atherosclerosis. Furthermore, vascular endothelial dysfunction has been linked to CSVD via increased blood–brain barrier permeability.[35 36] Oxidative stress induced by hyperglycemia and large glycemic variability decreases nitric oxide synthase activity and causes vascular endothelium dysfunction.[37–39] In fact, the results of this study showed that the severity of cerebral WMLs was associated with hyperglycemia indices, such as $TAR^{>250}$ and HBGI, and with GRI, an index of the quality of glycemic control. HBGI is an index that reflects the frequency and severity of hyperglycemia, and its value increases with higher blood glucose levels.[21] GRI is an index calculated from the CGM-derived TAR and TBR.[22] It is characterized by its emphasis on $TAR^{>250}$ rather than $TAR^{180\text{-}250}$ in the calculation of the hyperglycemia component, and as with the HBGI, the worse the degree and duration of hyperglycemia, the higher its value.[22] In the participants of this study, the GRI was mainly derived from HyperCompo because of the low $TBR^{<54}$. The severity of cerebral WMLs was particularly associated with $TAR^{>250}$, suggesting that risk indices, such as HBGI and GRI, are associated with the severity of cerebral WMLs. Furthermore, TIR is associated with diabetic microvascular and macrovascular complications,[17 40–43] which may explain why TIR was significantly associated with the severity of cerebral WMLs in this study.

In contrast to TIR and hyperglycemia indices (such as $TAR^{>180}$, $TAR^{>250}$, and HyperCompo), the present study showed that mean SG was not significantly associated with the severity of WMLs. Although mean SG has been reported to be highly correlated with TAR,[22 44] both hyperglycemia and hypoglycemia affect mean SG and HbA1c levels.[45] This study showed that there was no association between hypoglycemic indices and the severity of WMLs unlike hyperglycemia indices. Thus, the results of this study suggest that hyperglycemia indices might be more related to the severity of WMLs than mean SG. Although hypoglycemia has been reported to be linked to an increased dementia risk,[46] cerebral WMLs and MTA were not associated with hypoglycemic indices. This discrepancy could be due to small sample size, the participants in this study had low $TBR^{<54}$ and LBGI, and few participants had severe hypoglycemia. Thus, probably, significant association between hypoglycemic indices and alterations in brain structure was not revealed in this study. A larger study is required to investigate the association between

alterations in brain structure and mean SG and hypoglycemia indices.

The severity of cerebral WMLs was not significantly associated with CV, which is one of the glycemic variability indices. CVs of ≥36% increase the risk of hypoglycemia in type 1 diabetes.[17 19] A CV cut-off of 34.0% prevents hypoglycemia in patients with T2DM.[47] A study of patients with T2DM using FreeStyle Libre Pro (similar to the present study) reported a more conservative CV cut-off of 30.0% to avoid hypoglycemia.[29] However, it has been reported that the CV cut-off value increases as HbA1c decreases.[47] Therefore, in T2DM, CV targets may differ depending on diabetes medications and glycemic control status.[48] Thus, the association between cerebral WMLs and glycemic variability may be better evaluated using glycemic variability indices, such as mean amplitude of glycemic excursion and continuous overlapping net glycemic action.[49]

This study has several limitations. First, the number of patients with severe WMLs was small (49 subjects), which may have affected the validity of the logistic model.[50] Therefore, a larger-scale study is considered necessary. Second, the subject population was well glycemic controlled, as evidenced by median HbA1c, TIR, and TBR$^{<54}$ values of 7.0%, 77.9%, and 0%, respectively. The proportion of patients with HbA1c levels of ≥8.0 was small (12.7%) because only Japanese patients with T2DM under diabetologist's care were enrolled in this study. Although this study shows that WML severity and TIR and GRI are associated even in populations with good glycemic control, further investigations of CGM-derived glycemic control indices and brain imaging markers from more diverse populations are needed to indicate, further, the importance of this finding. Third, CV was used as an index of glycemic variability; however, there is no consensus in the cut-off value of CV in T2DM. Therefore, other glycemic variability indices may need to be investigated. Fourth, this is a cross-sectional study. Long-term prospective studies on the relationship between glycemic control indices and cerebral imaging markers are needed. Last, the generalizability of the findings may be limited because the participants in this study were older people from a specific urban area in Japan. Therefore, larger-scale studies are needed in the future.

In conclusion, the results of the present study show that cerebral WML severity is associated with hyperglycemic indices. Furthermore, cerebral WML severity is associated with TIR and GRI, which are indices of the quality of glycemic control. However, MTA is not significantly associated with CGM-derived TIR or GRI.

Author affiliations
[1]Department of Diabetes, Endocrinology and Clinical Immunology, School of Medicine, Hyogo Medical University, Nishinomiya, Hyogo, Japan
[2]Department of Radiology, School of Medicine, Hyogo Medical University, Nishinomiya, Japan

Acknowledgements The analysis of this study was supported by Professor Takashi Daimon, Department of Biostatistics, Hyogo Medical University (Japan). The authors are grateful for the excellent technical assistance of Misa Inamoto and Ai Matsumoto. The authors would like to thank Professor Koichiro Yamakado and the staff of the Department of Radiology, School of Medicine, Hyogo Medical University (Japan) for their cooperation in taking MRI scans. We would also like to thank the staff of the Department of Diabetes, Endocrinology and Clinical Immunology, School of Medicine, Hyogo Medical University, and the participants in this study for their valuable contributions.

Collaborators The members of the HDHCC study group are as follows: Yoshiki Kusunoki, Keiko Osugi, Mana Ohigashi, Chikako Inoue, Maki Inoue, Ayako Takagi, Chisako Yagi, Akiko Morimoto, Taku Tsunoda, Miki Kakutani, Akinori Kanzaki, Manabu Kadoya, Kosuke Konishi, Takuhito Shoji, Tomoyuki Katsuno, and Hidenori Koyama, Hyogo Medical University; Hiroyuki Konya and Toshihiro Matsuo, Ashiya Municipal Hospital; Hideki Ifuku, Amagasaki Chuo Hospital; Daisuke Azuma, Azuma Clinic; Takeshi Fukui, Fukui Clinic; Isao Hayashi, Hayashi Clinic; Satoru Katayama, Hyogo College of Medicine, Sasayama Medical Center; Masataka Kanyama, Masaru Usami, and Hiroki Ikeda, Ikeda Hospital; Tadahiro Inagaki, Inagaki Medical Clinic; Tomoya Hamaguchi, Itami City Hospital; Akihito Otsuka, Kawasaki Hospital; Shogo Kurebayashi, Kurebayashi Clinic; Kenji Kusunoki, Kusunoki Clinic; Minoru Kubota, Osaka University Graduate School of Medicine; Takeharu Sasaki, Nishinomiya Watanabe Hospital; Sachie Hirose, Satoshi Matsutani, and Shinya Makino, Osaka Gyoumeikan Hospital; Tetsuhiro Kitamura and Daisuke Tamada, Tamada Clinic; Hidenori Taniguchi, Taniguchi Medical Clinic; Nobuaki Watanabe, Watanabe Clinic; and Mitsuyoshi Namba, Takarazuka City Hospital.

Contributors CI, YK, KO, MO and HK designed this study and collected the participants, analyzed the data, and wrote the paper. AT, CY, MI, TT, MKak, MKad, KKo and TK recruited the participants for this study. KKi analyzed the brain images. All authors have approved the final manuscript. YK is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding This study was partly funded by the Japan Society for The Promotion of Science KAKENHI (Grants 22K10541 and 21K17297). This work was also funded by the "Hyogo Medical University Diversity Grant for Research Promotion" under MEXT Funds for the Development of Human Resources in Science and Technology, "Initiative for Realizing Diversity in the Research Environment (Characteristic-Compatible Type)".

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was performed in accordance with the Declaration of Helsinki guidelines. This study was approved by the Ethics Committee of Hyogo Medical University Hospital and the ethics review committee of each participating institution (Approval no. 4250). All participants provided informed consent and signed informed consent forms.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The individual de-identified participant data will be shared with the corresponding author upon reasonable request.

ORCID iD
Yoshiki Kusunoki http://orcid.org/0000-0002-9361-9317

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