博 士 学 位 論 文

早期の糖尿病患者においての血糖変動性と不十分な脂質管理が冠動脈の動脈硬化の中期的な進行に与える影響について：持続血糖測定器による分析

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論文題目

Glycemic variability and insufficient lipid control as predictors for mid-term progression of coronary atherosclerosis in patients with early diabetes : Analysis with serial continuous glucose monitoring

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記

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Doctoral Dissertation

Glycemic variability and insufficient lipid control as predictors for mid-term progression of coronary atherosclerosis in patients with early diabetes : Analysis with serial continuous glucose monitoring

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Glycemic variability and insufficient lipid control as predictors for mid-term progression of coronary atherosclerosis in patients with early diabetes: Analysis with serial continuous glucose monitoring

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ABSTRACT

Background : The incidence of coronary events is higher in patients with diabetes, even after statin therapy. Recently, glycemic variability assessed by continuous glucose monitoring (CGM) has been suggested to be associated with the progression of coronary atherosclerosis in these patients. Therefore, we prospectively followed patients using serial CGM and coronary angiography (CAG) over 10 months.

Methods and Results : This was a prospective observational study of 27 patients with coronary artery disease (CAD) and early stage diabetes (including impaired glucose tolerance). The progression of coronary artery percent stenosis by CAG was observed in 12 patients (the progression group). Assessment of baseline characteristics indicated that a higher mean amplitude of glycemic excursion (MAGE), an index of glycemic variability, was associated with disease progression (P = 0.023). Although low-density lipoprotein cholesterol (LDL-C) levels were significantly decreased during the 10 months, the progression group showed higher LDL-C at follow-up (P = 0.037). In addition, only patients without progression showed increased high-density lipoprotein cholesterol (HDL-C) during the 10 months. Consequently, a high LDL-C/HDL-C ratio at follow-up was associated with progression (P = 0.012). However, these were not associated with changes in plaque burden or necrotic core volume on virtual histology-intravascular ultrasound.

Conclusions : In Japanese patients with CAD and early stage diabetes receiving statin therapy, both glycemic variability (MAGE) at baseline and a high LDL-C/HDL-C ratio at follow-up were predictors for mid-term progression of coronary atherosclerosis. The strategies for modifying these predictors, and the effects on the progression of coronary atherosclerosis need to be explored further.

Trial registration : UMIN000014690

Key words : coronary artery disease; early diabetes; glycemic variability; HDL cholesterol; LDL cholesterol.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is strongly associated with coronary atherosclerosis and vascular complications, both of which are responsible for worse morbidity and mortality outcomes [1]. Optimal management in patients with diabetes includes pharmacological interventions and lifestyle modification, including diet, exercise, and weight loss. To reduce the risk of cardiovascular events, pharmacological therapy must not only target hyperglycemia but must also target hypertension, dyslipidemia, and thrombotic risk [2, 3]. A number of large trials in patients with dyslipidemia, including those with T2DM, have proven the efficacy of statins in reducing low-density lipoprotein cholesterol (LDL-C) levels and improving cardiovascular outcomes. Although patients with diabetes gain a significant relative risk reduction with statin therapy, they retain high residual cardiovascular risk even with optimization of plasma LDL-C concentrations [4]. It is possible that this is because of uncorrected atherogenic dyslipidemia or insufficient glycemic control.

Postprandial hyperglycemia and insulin resistance/hyperinsulinemia play critical roles in the development of diabetic atherosclerosis, especially in early stage T2DM, including impaired glucose tolerance (IGT) [5, 6]. Recent studies have indicated that glycemic variability was a significant predictor of mortality, and that it may play a role in the pathogenesis of atherosclerosis in patients with T2DM as well as in patients who are critically ill [7－9]. Glycemic variability implies both upward and downward acute changes in glucose－fluctuations in glucose levels－and is usually measured by continuous glucose monitoring (CGM) as the mean amplitude of glycemic excursion (MAGE) [10]. Some studies have showed that glycemic variability seemed to have more deleterious effects than sustained hyperglycemia in the development of diabetic complications, because acute glucose swings activate oxidative stress [11, 12]. However, we still do not understand the long-term influences of glycemic variability on cardiovascular disease in early T2DM, and equally, we are yet to resolve whether it interacts with other atherogenic factors such as uncorrected dyslipidemia.

In this prospective study, we aimed to determine whether glycemic variability substantially affected on the mid-term progression of coronary atherosclerosis in Japanese patients with early stage diabetes and coronary artery disease (CAD). To provide a detailed analysis, serial CGM and coronary angiography with virtual histology (VH) intravascular ultrasound (IVUS) were used. We also evaluated whether uncorrected atherogenic dyslipidemia after statin therapy might affect atherosclerotic progression.

METHODS

Study design

This was a prospective, single center, observational study. Eligible patients with early diabetes and CAD were followed for 10 months from August 2014 to July 2016 at Kindai University Hospital. The inclusion criteria were as follows: 1) age ≥ 20 years; 2) T2DM without insulin therapy or IGT; and 3) CAD where percutaneous coronary intervention (PCI) has been performed with a drug-eluting stent. The diagnosis of

diabetes was made by 75g oral glucose tolerance test or was assumed in those already taking antidiabetic drugs. IGT was also diagnosed by 75g oral glucose tolerance test.

Patients were excluded if they met the following criteria: 1) unstable hemodynamic status; 2) dialysis or severe renal insufficiency, defined as an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2; and 3) unsuitable for IVUS examination. Diagnostic coronary angiography (CAG) with IVUS was performed just after PCI, and follow-up CAG was also performed with IVUS at approximately 10 months. Biochemical markers including CGM, urinalysis, echocardiography, endothelial function, and platelet function were assessed just after PCI; and the biochemical markers and urinalysis were reassessed at the time of follow-up CAG.

The study protocol was approved by the Ethics Committee of Kindai University Faculty of Medicine. Written informed consent was obtained from all patients. The trial was registered at http://www.umin.ac.jp under UMIN000014690.

Measurement of biochemical and urinary parameters, endothelial and platelet functions

The following parameters were measured at baseline (after PCI) and follow-up CAG (10 months after PCI) : standard urinalysis, urinary albumin, complete blood count, serum electrolytes, liver function, renal function, lipid profile (including a ratio of serum eicosapentaenoic acid to arachidonic acid; EPA/AA), high-sensitivity c-reactive protein (hs-CRP), immunoreactive insulin (IRI), 1,5-anhydroglucitol (1,5AG) and glycated hemoglobin (HbA1c). The patients with α-glucosidase inhibitors were excluded for the assessment of 1,5AG. At baseline (after PCI), as described previously, we assessed peripheral endothelial function by reactive hyperemia-peripheral arterial tonometry using an EndoPAT2000 (Itamar Medical, Caesarea, Israel), and we assessed ex vivo platelet function during dual antiplatelet therapy by the VerifyNow P2Y12 assay (Accumetrics, Inc., San Diego, California), [13, 14]. The reactive hyperemia index (RHI) was calculated to assess endothelial function, and the P2Y12 reaction unit (PRU) and percentage inhibition index (derived from the simulated baseline response induced by thrombin receptor-activating peptide) were calculated to assess platelet function. The eGFR was calculated using an equation specific to the Japanese population: eGFR = 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$ (× 0.739 if female) [10]. Albuminuria was determined by the urinary albumin-to-creatinine ratio (UACR). Microalbuminuria was defined as a UACR of 30–299 mg/g creatinine, and overt albuminuria as a UACR of ≧ 300mg/g creatinine. The homeostasis model assessment-insulin resistance (HOMA-IR) value was calculated using the following formula: HOMA-IR = [fasting insulin (μIU/ml) × fasting glucose (mg/dl)]/ 405.

CGM analysis

All patients were equipped with a CGMS (iPro2; Medtronic, Minneapolis, USA) at baseline and follow-up CAG and monitored for at least 24 consecutive hours, as previously described [9]. At baseline, the patients

with acute myocardial infarction were equipped with a CGMS in the stable phase at least 7 days after PCI, while the other patients were done at one day after PCI. The glucose profile and glucose excursion parameters were analyzed using CareLink iPro software, and the MAGE was calculated by measuring the arithmetic mean of the differences between consecutive peaks and nadirs, provided that the difference was > 1 standard deviation (SD) of the mean glucose value, using the EasyGV software (https://www.phc.ox.ac.uk/research/technology-outputs/easygv)[15]. Hypoglycemia was defined as any blood glucose level less than 70 mg/dL.

Coronary angiography and IVUS analysis

Progression of coronary atherosclerosis was evaluated in non-culprit lesions for PCI by comparison of the percent stenosis between the baseline and follow-up CAG. Patients received intracoronary isosorbide dinitrate (1-5 mg) before their initial angiograms to achieve maximal vasodilation and CAG was obtained in routine standardized projections. Quantitative coronary angiography was performed for all qualifying angiograms using CAAS II (Pie Medical Imaging, Maastricht, The Netherlands). Progressive coronary atherosclerosis was defined as the presence of any of the following: ≥ 10% reduction in the diameter of a pre-existing ≥ 50% stenosis; ≥ 30% reduction in the diameter of a < 50% stenosis; development of a new stenosis with ≥ 30% reduction in the diameter of a segment that was normal on baseline CAG; or progression of any lesion to total occlusion on follow-up CAG [9, 16]. Patients were divided into two groups by the presence or absence of atherosclerotic progression.

Baseline IVUS examination was performed on both the distal and proximal sides of culprit lesions after PCI. An Eagle Eye Gold IVUS catheter (Volcano, San Diego, USA) was used with a motorized pullback device to withdraw the transducer at 0.5 mm/s. During pullback, grayscale IVUS images were recorded, and raw radiofrequency data were captured at the top of the R-wave by using a commercially available IVUS console (IVG3; Volcano). At follow-up CAG, the IVUS examination was repeated in the same coronary artery. Baseline and follow-up IVUS images were reviewed side-by-side on a standard display, and the distal and proximal ends of the target segment were identified by reproducible anatomic landmarks such as side branches, veins, and the stent edges. Plaques close to the PCI site (within 5 mm) were excluded. Quantitative grayscale IVUS analysis was performed according to the guidelines of the American College of Cardiology and European Society of Cardiology [17]. VH-IVUS data analysis was based on calculation of grayscale border contour, and relative and absolute amounts of different coronary artery plaque components were measured using IVUSLab version 2.2 (Volcano Corporation). On the VH-IVUS images, fibrous tissue was marked in green, fibrofatty tissue in yellow, dense calcium in white, and necrotic cores in red[18]. Thin-cap fibroatheroma(TCFA) by VH-IVUS was defined as previously described [19].

Statistical analysis

Categorical variables were compared using the χ^2 test for proportions and the unpaired t-test or Mann-Whitney U test for continuous variables, as appropriate. Overall differences between baseline and follow-up CAG were determined using repeated measures analysis of variance. Factors considered predictors of atherosclerotic progression were analyzed using a receiver operating characteristics (ROC) curve analysis, and the sensitivities and specificities of the cut-off levels were calculated. Further multiple logistic regression analysis was performed to define independent variables that might predict the progression of coronary atherosclerosis. All P-values < 0.05 were considered statistically significant. Results are expressed as mean ± SD. All analyses were performed using JMP version 12.2.

RESULTS

Baseline clinical characteristics and laboratory findings

Of the 27 patients enrolled, 3 were excluded because they refused to undergo the follow-up CAG. The baseline characteristics of the remaining 24 participants are shown in Table 1. Most were male (75.0%) and aged over 65 years (70.8%), and the mean blood pressure were acceptable. We diagnosed 41.7% of patients having IGT and the remaining 58.3% as having T2DM. PCI was performed in 14 patients with acute coronary syndrome (ACS) and 10 patients with stable CAD. Overall, 58.3% of the patients only received life-style interventions, while the remainder received oral hypoglycemic drugs; the most common agents were dipeptidyl peptidase-4 inhibitors (66.6%), followed by α-glucosidase inhibitors (12.5%) and sulfonylureas (12.5%). At baseline, statins were administrated to half of the patients.

At follow-up period, 3 patients had started oral hypoglycemic therapy, and 6 had their dosages increased or had additional drugs added to their regimens. All patients except one were receiving statins; thus, 45.8% of all participants were started on statin therapy during follow-up. Moreover, 16.7% of patients already receiving a statin required an increased dosage or had an additional anti-hyperlipidemic drug added to their regimen.

At baseline, HbA1c, 1,5-AG and fasting blood glucose were 6.31% ± 0.70%, 15.5 ± 8.8 μg/mL and 104.0 ± 25.6 mg/dL, respectively; interestingly, none of these parameters had changed by 10 months (Table 2). However, there were significant changes in LDL-C, high-density lipoprotein cholesterol (HDL-C) levels, and the EPA/AA ratio. In addition, uric acid, hs-CRP, and eGFR levels decreased significantly during the study period. In the CGM analysis, the mean plasma glucose, SD of mean plasma glucose, and MAGE had not changed significantly by 10 months (Table 3).

Table 1. Baseline clinical characteristics

	N = 24
Age（years）	68.0 ± 9.4（37–88）
Male（%）	75
BMI（kg/m^2）	24.1 ± 3.1
Blood pressure（systolic/diastolic）（mmHg）	128.2 ± 19.2/74.4 ± 18.5
T2DM / IGT	14/10
Diabetes duration（years）	1.95（IQR: 0 －2.29）
ACS / stable CAD	14/10
Hypertension（%）	83.3
Dyslipidemia（%）	87.5
Current smoking（%）	12.5
Obesity（BMI ≥ 25）（%）	29.1
Hyperuricemia（≥ 7.0 mg/dL）（%）	0
Oral hypoglycemic drugs（%）	41.7
ACEI / ARB（%）	58.3
Calcium channel blocker（%）	29.2
Beta-blocker（%）	41.7
Statin（%）	50.0

Values are the mean ± SD, number or %.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; IGT, impaired glucose tolerance; IQR, interquartile rage; T2DM, type 2 diabetes mellitus.

Table 2. Serial changes in laboratory parameters

	Baseline	10 months	P value
Body weight (kg)	62.8 ± 9.0	63.1 ± 10.1	0.720
HbA1c (%)	6.31 ± 0.70	6.46 ± 0.73	0.070
1.5-AG (μg/mL)	15.5 ± 8.8	16.8 ± 9.9	0.230
FBG (mg/dL)	104.0 ± 25.6	104.7 ± 22.6	0.781
IRI (IU)	6.62 ± 3.94	6.84 ± 4.03	0.759
HOMA-R	1.71 ± 1.05	1.86 ± 1.35	0.395
Insulin resistance (HOMA-R ≥ 2.5) (%)	12.5	16.7	
LDL-C (mg/dL)	122.7 ± 33.3	90 ± 28.3	0.001
HDL-C (mg/dL)	50.6 ± 11.8	57.3 ± 15.5	0.015
Triglyceride (mg/dL)	136.6 ± 83.3	136.6 ± 69.0	0.584
EPA / AA	0.31 ± 0.13	0.39 ± 0.25	0.044
Uric acid (mg/dL)	4.76 ± 1.37	5.23 ± 1.33	0.037
hs-CRP (mg/dL)	0.13 ± 0.13	0.06 ± 0.04	0.021
Cr (mg/dL)	0.75 ± 0.23	0.81 ± 0.19	0.017
eGFR (mL/min/1.73 m^2)	77.2 ± 18.8	69.8 ± 14.4	0.012
UACR (mg/g Cr)	15.3 ± 24.9	19.9 ± 41.0	0.380
Microalbuminuria or overtalbuminuria (%)	12.5	12.5	

Values are the mean ± SD or %.
Abbreviations: 1,5AG, 1,5-anhydroglucitol; Cr, Creatinine; eGFR, estimated glomerular filtration rate; EPA/AA, a ratio of serum eicosapentaenoic acid to arachidonic acid; FPG, fasting blood glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity c-reactive protein; HOMA-R, homeostasis model assessment-insulin resistance; IRI, immunoreactive insulin; LDL-C, low-density lipoprotein cholesterol; UACR, urinary albumin-to-creatinine ratio.

Table 3. Serial changes in continuous glucose monitoring parameters

	Baseline	10 months	P Value
Mean blood glucose (mg/dL)	124.9 ± 26.8	121.0 ± 22.4	0.373
SD (mg/dL)	27.4 ± 13.7	27.1 ± 10.9	0.907
MAGE (mg/dL)	62.3 ± 31.5	59.4 ± 24.1	0.665
CONGA (mg/dL)	108.9 ± 24.7	108.9 ± 20.9	0.331
% time at < 70 mg/dL (%)	23.4 ± 20.6	22.3 ± 22.04	0.757
% time at ≥ 140 mg/dL (%)	2.83 ± 5.32	3.04 ± 4.90	0.822
Patients with hypoglycemia (%)	41.7	62.5	0.248

Values are the mean ± SD or %.
Abbreviations: CONGA, continuous overlapping net glycemic action; MAGE, mean amplitude of glycemic excursion; SD, standard deviation of mean blood glucose.

Comparisons between the patients with and without progression

The CAG findings and PCI procedures at baseline are shown in Table 4. All patients underwent PCI with a drug-eluting stent and had no perioperative complications. Follow-up CAG was after 10.5 ± 2.7 months, and 12 (50%) of the patients evidenced progression of coronary atherosclerosis in non-culprit lesions; 2 had ≥ 10% reductions in the diameter of a pre-existing ≥ 50% stenosis, 5 had ≥ 30% reductions in the diameter of < 50% stenosis, and 5 had development of a new stenosis with ≥ 30% reduction in the diameter of a normal segment. Only 8.3% of patients needed a repeat PCI for binary restenosis in the culprit lesion. No major cardiovascular events were observed during the study period.

Table 4. Coronary angiographic findings

	N = 24
Treated coronary vessel	
Left anterior descending, (%)	37.5
Left circumflex, (%)	25.0
Right coronary, (%)	37.5
Number of diseased vessels	1.5 ± 0.7
Culprit lesion for DES (%)	100
ACC/AHA type classification; A/B1/B2/C (%)	33.3/8.3/37.5/20.9
Stent diameter (mm)	3.06 ± 0.43
Stent length (mm)	20.4 ± 7.6
Angiographic follow-up period (month)	10.5 ± 2.7
Binary restenosis in the culprit lesion (%)	8.3

Values are the mean ± SD or %.
Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; DES, drug-eluting stent.

We observed no significant differences between patients with and without atherosclerotic progression in terms of baseline clinical characteristics, including the prevalence of ACS, stable CAD, T2DM, or IGT. Among the baseline laboratory findings, only the HbA1c level was significantly higher in patients with progression (Figure 1). The baseline IRI, HOMA-R, EPA/AA ratio, eGFR, hs-CRP level, and RHI in the reactive hyperemia-peripheral arterial tonometry analysis were not different between the groups. Also, the PRU was not different between the groups (168.7 ± 52.7 in non-progression group and 171.6 ± 54.6 in the progression group; P = 0.895). At follow-up, there was no significant difference in HbA1c, IRI, HOMA-R, EPA/AA ratio, eGFR, and hs-CRP level. By contrast, although a significant decrease was observed in the progression and non-progression groups over 10 months, a higher LDL-C level was observed in patients with progression (P = 0.037). However, HDL-C only increased among the patients without progression over the 10 month period, so there

was a higher LDL-C/HDL-C ratio in the patients with progression (P = 0.012).

In the CGM analysis, only MAGE was significantly higher at baseline in patients with progression (Figure 2). At follow-up, no significant differences were observed between the groups in any parameter, including MAGE. Also, no serial changes were observed in each group. The time spent with a blood glucose < 70 mg/dL (as a percent of the total time) and the number of patients with hypoglycemia did not differ between the groups at either baseline or follow-up.

Among the baseline measurements, ROC analysis showed that the area under the ROC curve (AUC) for MAGE as an indicator of atherosclerosis progression was 0.778 (95% CI; 0.577－0.978) (Figure 3). The optimal cut-off value was 45.4 mg/dL, with a sensitivity of 100% and a specificity of 67%. Among the follow-up measurements, the AUC for a high LDL-C/HDL-C ratio as an indicator of atherosclerosis progression was 0.806 (95% CI; 0.625–0.988), and the optimal cut-off value was 1.84 with a sensitivity of 67% and a specificity of 92%. Multivariable regression analysis revealed that the baseline MAGE and follow-up LDL-C level were both independent predictors of atherosclerosis progression (P = 0.012 and P = 0.044, respectively). The fit (R^2) of the model was 0.306. In the model of the baseline MAGE and follow-up LDL-C/HDL-C ratio, only LDL-C/HDL-C ratio was a significant predictor of atherosclerosis progression (P = 0.084 and P = 0.029, respectively). The fit (R^2) of the model was 0.327.

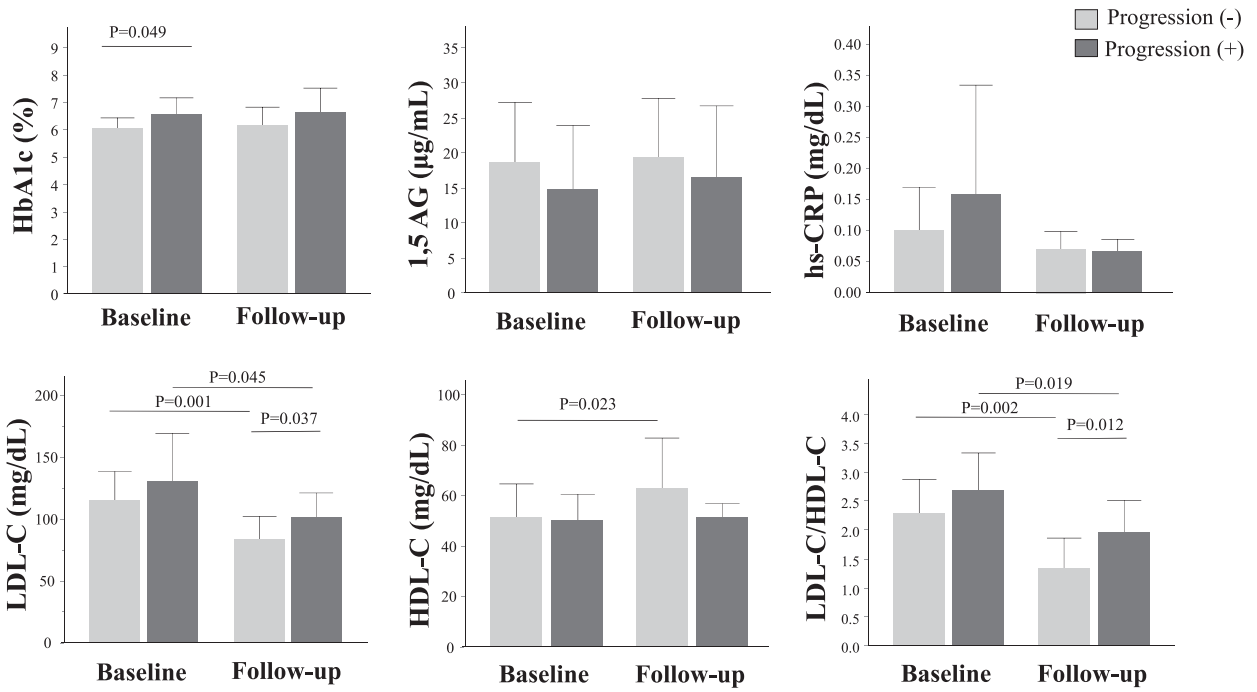

Figure 1. Serial changes in laboratory findings between patients with and without atherosclerosis progression
Abbreviations: 1,5AG, 1,5-anhydroglucitol; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitive c-reactive protein; LDL-C, low-density lipoprotein cholesterol. The values are means ± SD.

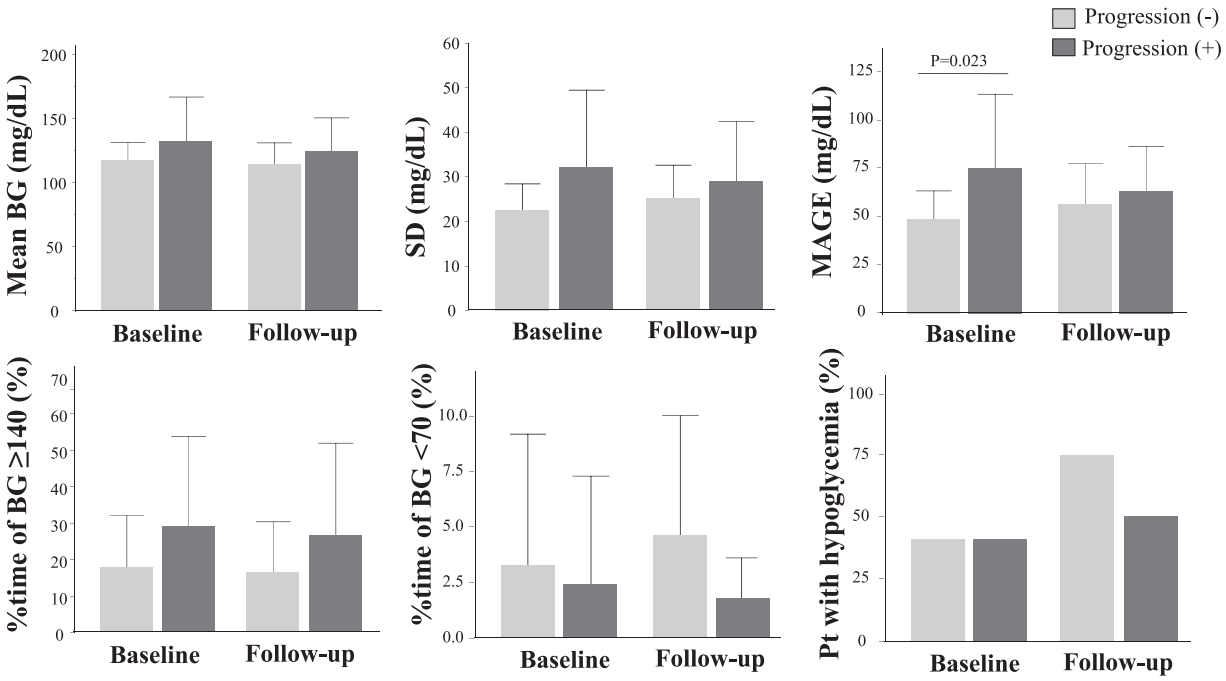

Figure 2. Serial changes in continuous glucose monitoring parameters between patients with and without progression
Abbreviations: BG, blood glucose; MAGE, mean amplitude of glycemic excursion; Pt, patients; SD, standard deviation of mean blood glucose.

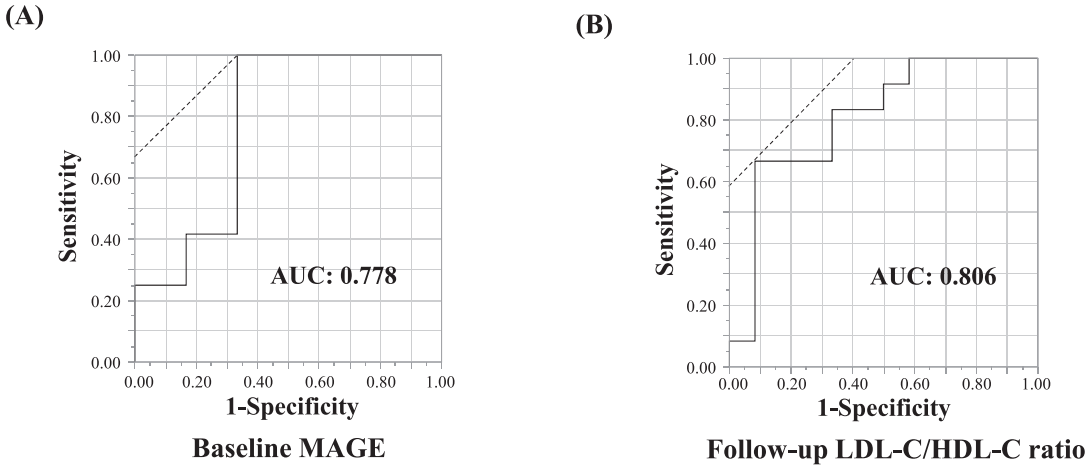

Figure 3. Receiver operating characteristic curves for indicators of atherosclerotic progression
Abbreviations: AUC, area under the ROC curve; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MAGE, mean amplitude of glycemic excursion.

Grayscale and VH-IVUS analysis

Serial measurements by grayscale IVUS and VH-IVUS are summarized in Table 5. In the baseline and follow-up analyses, no significant differences were observed in any of the parameters, except for the percentage fibrofatty volume (%FF) between patients with and without progression. In the patients with progression, there were no increases during the study in plaque volume index (PVI) or plaque burden (%PVI) by grayscale IVUS or in necrotic core volume index (NCVI), fibrofatty volume index (FVI), or the number of TCFAs by VH-IVUS. Furthermore, both the baseline MAGE and the follow-up LDL-C/HDL-C ratio were not associated with changes in PVI, %PVI, NCVI, or FVI (Figure 4). When patients were divided into those with PVI progression (%PVI change > 0%) and those without, baseline MAGE and follow-up LDL-C/HDL-C ratio were not different between the groups (P = 0.175 and P = 0.525, respectively). The same was true when patients were divided into those with NCVI progression (NCVI change > 0%) and those without (P = 0.624 and P = 0.931, respectively).

Table 5. Serial changes in grayscale IVUS and VH-IVUS measurements

	Progression (-)			Progression (+)			P value between groups	
	Baseline	Follow-up	P value	Baseline	Follow-up	P value	Baseline	Follow-up
Grayscale IVUS								
VVI (mm^3/mm)	15.8 ± 6.2	16.8 ± 6.0	0.018	14.6 ± 3.9	14.5 ± 4.1	0.822	0.578	0.292
LVI (mm^3/mm)	7.7 ± 2.9	8.1 ± 2.6	0.140	7.8 ± 1.6	7.8 ± 1.7	0.870	0.869	0.741
PVI (mm^3/mm)	8.0 ± 3.7	8.2 ± 4.1	0.428	6.7 ± 2.6	6.7 ± 2.8	0.937	0.344	0.307
%PVI (%)	49.4 ± 10.1	47.1 ± 11.2	0.366	45.2 ± 6.0	45.0 ± 7.8	0.833	0.233	0.604
Lesion length (mm)	39.6 ± 18.7	39.6 ± 18.7	0.261	49.7 ± 14.1	49.7 ± 14.1	0.582	0.147	0.148
VH-IVUS								
NCVI (mm^3/mm)	1.2 ± 0.8	1.1 ± 0.8	0.278	0.7 ± 0.6	0.8 ± 0.6	0.172	0.127	0.313
%NC (%)	21.4 ± 7.8	21.2 ± 6.4	0.915	16.3 ± 5.6	18.5 ± 4.3	0.110	0.078	0.239
FFVI (mm^3/mm)	0.5 ± 0.3	0.6 ± 0.5	0.115	0.4 ± 0.2	0.4 ± 0.3	0.572	0.743	0.316
%FF (%)	9.3 ± 3.5	10.2 ± 0.5	0.567	13.1 ± 5.1	10.7 ± 4.4	0.024	0.046	0.786
FIVI (mm^3/mm)	2.9 ± 1.8	3.0 ± 2.0	0.894	2.3 ± 1.3	2.3 ± 1.5	0.576	0.320	0.387
%FI (%)	60.1 ± 10.0	59.2 ± 8.8	0.534	64.4 ± 7.1	62.8 ± 8.7	0.267	0.228	0.320
DCVI (mm^3/mm)	0.5 ± 0.5	0.5 ± 0.1	0.182	0.3 ± 0.2	0.4 ± 0.1	0.280	0.125	0.522
%DC (%)	9.2 ± 6.3	9.4 ± 7.0	0.809	6.2 ± 4.5	8.0 ± 7.2	0.249	0.193	0.637
VH-TCFAs (n)	5	5		4	4			

Values are the mean ± SD, number or %.

Abbreviations: DC, dense calcium; DCVI, dense calcium volume index; FF, fibrofatty; FFVI, fibrofatty volume index; FI, fibrous; FIVI, fibrous volume index; IVUS, intravascular ultrasound; LVI, lumen volume index; NC, necrotic core; NCVI, necrotic core volume index; PVI, plaque volume index; %PVI, plaque volume index divided by vascular volume index; TCFA, thin-cap fibroatheroma; VH-IVUS, virtual histology-intravascular ultrasound; VVI, vascular volume index.

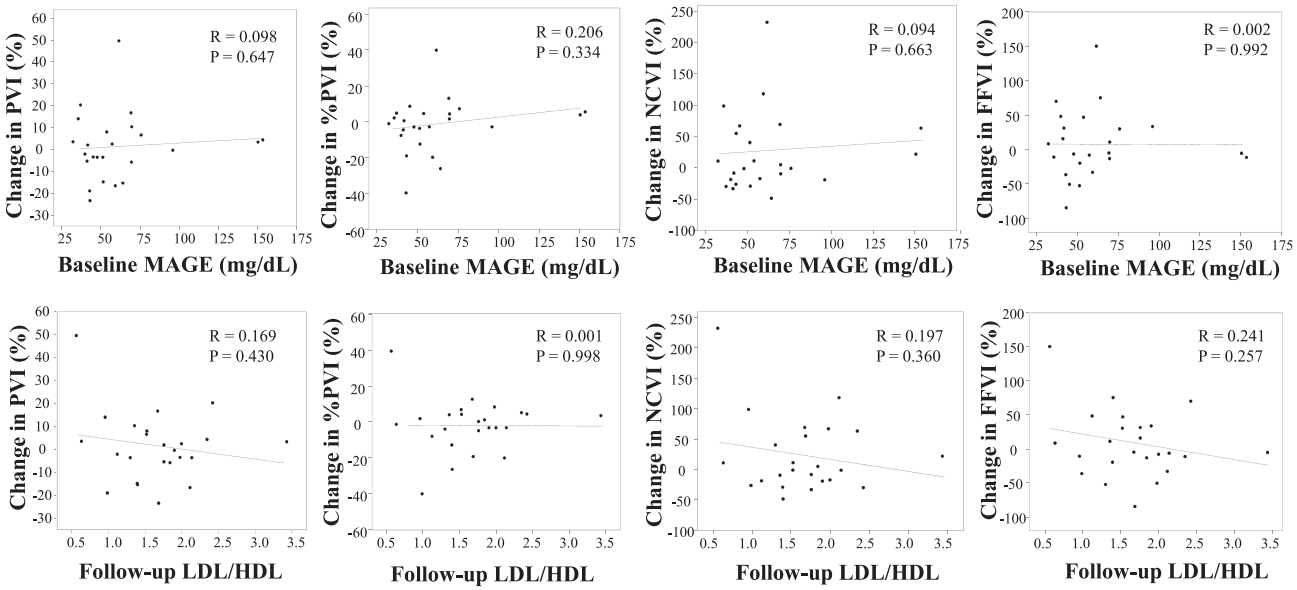

Figure 4. Correlations between baseline MAGE or follow-up LDL/HDL ratio and IVUS measurements
Abbreviations: FFVI, fibrofatty volume index; NCVI, necrotic core volume index; PVI, plaque volume index; %PVI, plaque volume index divided by vascular volume index.

DISCUSSION

CGM analysis in CAD

Postprandial glucose excursions are considered to have potentially deleterious effects in the development of diabetic atherosclerosis because of their association with increased oxidative stress. CGM provides a more complete view of these glycemic excursions, including their duration and frequency, which allows for the calculation and assessment of objective features of glycemic variability.

Recently, several studies using CGM have indicated that glycemic variability was a significant predictor of major adverse cardiac events (MACE), coronary atherosclerosis progression, and plaque vulnerability [8, 9, 20]. Su et al. reported that, in 222 patients with acute myocardial infarction, higher MAGE on admission was a sensitive predictor of MACE at 12 months when compared with admission glucose or HbA1c level [8]. In other research, Kataoka et al. showed that MAGE early after the onset of ACS and hs-CRP at 1 month were independent predictors of coronary atherosclerosis progression in 88 patients with ACS and either DM, IGT, or normal glucose tolerance [9]. Although our participants were slightly different (i.e., ACS and stable CAD with T2DM or IGT), we similarly found that a higher MAGE at baseline was a significant predictor of coronary atherosclerosis progression. However, when we performed follow-up CGM after 10 months, neither follow-up MAGE nor serial change in MAGE was associated with atherosclerosis progression. Although the reason for lack of impact of MAGE at follow-up is unclear, MAGE may fluctuate more readily so may only have a small impact on the mid-term progression of coronary atherosclerosis. Kuroda et al. reported a significant association between MAGE and the relative amount of necrotic core or the presence of TCFAs in 70 patients with stable CAD and either diabetes, IGT, or normal glucose tolerance [20]. By contrast,

we observed no associations between baseline MAGE and either plaque burden (%PVI), relative amount of necrotic core, or TCFA by IVUS. This might be due to differences in the site of IVUS analysis, because we did not analyze plaques themselves, but the areas distal and proximal to the lesion. Further studies using IVUS for entire coronary arteries may be useful.

Lipid profile change on atherosclerosis progression

A number of large trials in patients with dyslipidemia, including those with diabetes, have proven the efficacy of statins in reducing LDL-C and in improving cardiovascular outcomes. However, patients with T2DM still have more coronary events compared to those without T2DM [21]. Thus, T2DM might accelerate plaque progression despite statin therapy, suggesting that stricter cholesterol management may be necessary [22].

In the present study, serial cholesterol measurements showed that a higher LDL-C/HDL-C ratio at follow-up was associated with atherosclerosis progression even when there was no difference at baseline; in patients with progression, both insufficient LDL-C reduction and a lack of increase in HDL-C were observed. Kataoka et al. reported that a substantial proportion of their patients with CAD failed to achieve effective reductions in LDL-C despite appropriate statin therapy, where greater progression of atherosclerosis was observed [23]. Also, a pooled analysis of 1,455 statin-treated patients enrolled in four clinical trials with IVUS revealed that raising HDL-C with statin therapy by an average of 7.5% was an independent predictor of the ability of a statin to slow progression of coronary atherosclerosis [24]. Similar findings were observed in patients with early diabetes in the present study. Furthermore, according to our multivariate analysis, the effect of higher LDL-C/HDL-C ratio on the mid-term progression of coronary atherosclerosis may be stronger than that of higher MAGE at baseline. Other lipid or inflammatory factors may influence the progression of coronary atherosclerosis [25], so further studies are necessary to elucidate the modifiable targets in these population.

Clinical implications

Our data provide insight into how lipid control affects atheroma progression in early diabetes. The obtained results are consistent with the observation that the greatest clinical benefit from the medical management of diabetes is derived from optimizing lipid control or from targeting associated risk factors; indeed, these seem much more likely to be cardioprotective than controlling glucose level alone [3, 26]. Thus, more careful and strict management of LDL-C and HDL-C levels is necessary to control the progression of coronary atherosclerosis and to offer prevention against cardiovascular events. In addition, the observation of accelerated disease progression in patients despite the use of blood pressure and lipid-modifying therapies may support the merit of controlling glycemic variability rather than simply targeting HbA1c. Moving forward, optimal strategies for increasing HDL-C and decreasing MAGE require further exploration.

Study limitations

Several limitations should be considered when interpreting our results. First, the study population was small, so any negative findings could be caused by the resulting low statistical power. Second, this was a single center study with inherent limitations, such as selection and referral biases. Third, most of the participants had early stage mild diabetes (83.3% had an HbA1c < 7.0%) and higher age (70.8% were aged > 65 years), meaning that our results cannot be extrapolated to all patients with diabetes and CAD. Lastly, whereas most studies have explored the mechanism of coronary atherosclerosis progression in diabetes in patients with either ACS or stable CAD. We included both patients with ACS and stable CAD. However, no differences were observed in baseline characteristics between the groups, including MAGE, HbA1c, LDL-C, HDL-C, and hs-CRP, and coronary atherosclerosis progression was observed equally in each group. Thus, the impact of ACS or stable CAD on the present results may be limited.

Conclusions

We conducted a prospective observational study of 24 patients with early diabetes and CAD, and followed them up with serial CAG and CGM for 10 months. In the CGM analysis, only a higher MAGE at baseline was associated with the progression of coronary atherosclerosis, as defined by progression of percent stenosis on CAG. Also, although the LDL-C level was significantly decreased during the 10 months of the study, a higher LDL-C/HDL-C ratio at follow-up was associated with atherosclerosis progression. We conclude that, in Japanese patients with CAD and early stage diabetes receiving statin therapy, both baseline glycemic variability (using MAGE) and a follow-up high LDL-C/HDL-C ratio could be used to predict mid-term progression of coronary atherosclerosis. Further studies are needed to explore these factors and their effects on the progression of coronary atherosclerosis, as well as how they can be modified.

Abbreviations

ACS, acute coronary syndrome; 1,5AG, 1,5-anhydroglucitol; AU, albuminuria; CAD, coronary artery disease; CAG, coronary angiography; CGM, continuous glucose monitoring; T2DM, type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate; EPA/AA, a ratio of serum eicosapentaenoic acid to arachidonic acid; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; hs-CRP, high-sensitivity c-reactive protein; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; MAGE, mean amplitude of glycemic excursion; PCI, percutaneous coronary intervention; PRU, P2Y12 reaction units; RHI, reactive hyperemia index; ROC, receiver operating characteristics; SD, standard deviation; TCFA, thin-cap fibroatheroma; UACR, urinary albumin-to-creatinine ratio; VH-IVUS, virtual histology intravascular ultrasound.

Competing interests

Shunichi Miyazaki received the research funding from the following companies; MSD, Daiichi-Sankyo, Otsuka, Boehringer Ingelheim, Astellas Pharma companies.

Authors' Contributions

The contribution of each author on this work was as follows: Kosuke Fujita and Yoshitaka Iwanaga: the idea and design of the study, analysis of the data, and writing of the paper. Masafumi Ueno and Tomoyuki Ikeda: data sampling and analysis. Shunichi Miyazaki: the idea and design of the study, interpretation of data, and writing of the paper.

Conflicts of interest

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

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