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Impact of daily glucose fluctuations on cardiovascular outcomes after percutaneous coronary intervention for patients with stable coronary artery disease undergoing lipid-lowering therapy

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ABSTRACT

Aims/Introduction: Glucose fluctuation (GF) is a residual risk factor for coronary artery disease (CAD). We investigated whether GF influenced clinical outcomes and progression of coronary stenosis in stable CAD patients.

Materials and Methods: In this prospective study, 101 consecutive lipid-controlled stable CAD patients underwent percutaneous coronary intervention were enrolled, and GF was expressed as the mean amplitude of glycemic excursion (MAGE) obtained by continuous glucose monitoring before the procedure was evaluated. At 9 months after enrollment, culprit and non-culprit (mild-to-moderate stenosis without ischemia) lesions were serially assessed by angiography. Cardiovascular events (CVE) consisting of cardiovascular death, non-fatal myocardial infarction or ischemia-driven revascularization during 2-year follow up, rapid progression in non-culprit lesions (defined as ≥10% luminal narrowing progression in lesions with stenosis ≥50%, ≥30% luminal narrowing progression in non-culprit lesions with stenosis <50% or normal segment, or progression to total occlusion) were evaluated.

Results: CVE occurred in 25 patients, and MAGE was significantly higher in the CVE group (76.1 ± 24.8 mg/dL vs 59.3 ± 23.7 mg/dL; $P = 0.003$). Multivariate analysis showed that MAGE was an independent predictor of CVE (odds ratio 1.027, 95% confidence interval 1.008–1.047; $P = 0.005$). The optimal MAGE value to predict CVE was 70.7 mg/dL (area under the curve 0.687, 95% confidence interval 0.572–0.802; $P = 0.005$). Furthermore, MAGE was independently associated with rapid progression, and with the luminal narrowing progression in all non-culprit lesions ($r = 0.400$, $P < 0.05$).

Conclusions: Daily GF might influence future CVE in lipid-controlled stable CAD patients.

INTRODUCTION

The beneficial effects of statins used as lipid-lowering therapy for the prevention of coronary artery disease (CAD) have been shown in numerous clinical trials[1-3]. However, the risk reduction was insufficient; therefore, the management of residual coronary risks has been investigated to improve the prognosis of CAD patients[4]. Diabetes mellitus has been known as a major aggravating factor for CAD in the era of universal statin use[5,6]. As postprandial hyperglycemia has long been known as one of the risk factors of CAD, glucose fluctuation is currently attracting attention[7]. Over the past decade, continuous glucose monitoring (CGM) systems have been widely used, and enable daily

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glucose fluctuations in clinical settings to be evaluated. Recent studies showed that patients with higher glucose fluctuations in acute coronary syndrome (ACS) had worse cardiovascular prognosis; furthermore, these fluctuations are also associated with rapidly progressive stenosis in the non-culprit artery in such patients[8,9]. Our previous observational studies suggested that glucose fluctuations might be associated with plaque vulnerability, which is involved in the occurrence of cardiovascular events (CVEs) in stable CAD patients undergoing lipid-lowering therapy[10-13]. However, the clinical impact of glucose fluctuations in those with stable CAD remains unclear.

The aim of the present study was to investigate whether mean amplitude of glycemic excursion (MAGE) is associated with future CVE and plaque progression expressed as rapid progression (RP) of non-culprit lesions, even in stable CAD patients undergoing lipid management after percutaneous coronary intervention (PCI).

METHODS

Study design

The present single-center, prospective, observational follow-up study was carried out at the Kobe University Hospital, Kobe, Japan, from July 2012 to February 2018. The present study was approved by the ethics committee of Kobe University, and written informed consent was obtained from all enrolled patients. This study was carried out according to the guidelines of the Declaration of Helsinki, and registered in the UMIN clinical trial registry (UMIN000021228).

Participants

A total of consecutive 101 stable CAD patients who underwent PCI to the culprit lesion and met the following criteria were enrolled from July 2012 to February 2016. The inclusion criteria were as follows: (i) being aged 20–85 years; and (ii) under lipid-lowering management, with low-density lipoprotein cholesterol <120mg/dL with statins, or <100mg/dL without statins, as in our previous study[10]. The exclusion criteria were as follows: (i) ACS; (ii) reduced left ventricular ejection fraction (<35%) or cardiogenic shock; (iii) concomitant inflammatory conditions or malignancies; and (iv) hemodialysis. The definition of patients with stable CAD was as follows: patients with clinical syndrome characterized by effort chest discomfort, including shoulder or back pain, and relieved at rest or after nitroglycerin use, or characterized by ischemic signs on examination of asymptomatic patients[14].

Protocol

After admission, fasting blood samples were collected the following morning, and a 75-g oral glucose tolerance test was carried out. Plasma glucose and immunoreactive insulin levels were evaluated before and every 30 min to 2 h after oral glucose load. Patients were classified into three groups based on 75-g oral glucose tolerance test results, as in our previous study[10,11]: normal glucose tolerance (NGT); impaired glucose tolerance and type 2 diabetes mellitus. Subcutaneous interstitial glucose levels using CGM system (iPro2; Medtronic, Northridge, CA, USA) were monitored over a period of three consecutive days. After these examinations, all patients underwent PCI to treat the culprit lesions. All patients were recommended to take dual antiplatelet agents – combination acetylsalicylic acid (100 mg/day) and thienopyridine (clopidogrel 75 mg/day or prasugrel 3.75 mg, according to Japanese recommendations) – for at least 12 months after PCI. The scheduled coronary angiography (CAG) was carried out at 9-month (±3) follow up after index PCI, and the incidence of CVE was evaluated during 2 years. If patients were readmitted for worsening angina or ACS, then CAG was carried out earlier than scheduled.

Analysis of CGM system

For all patients, the daily glucose profile was analyzed offline using data obtained on the middle days (day 2 or 3) to avoid any bias at the timing of insertion or removal of the sensor. The CGM analysis software calculated the 24-h mean glucose levels, the time in hyperglycemia (>140 mg/dL)/hypoglycemia (<70 mg/dL) and the MAGE, which represented fluctuations in blood glucose levels over a 24-h period[15]. All patients ate optimal meals during CGM, as in our previous report[10].

Evaluation of CAD

CAG was carried out after direct intracoronary injection of 2.5 mg isosorbide dinitrate by experienced cardiologists at the timing of the index PCI and the follow up. All angiograms were reviewed and analyzed using quantitative CAG (QAngio XA 7.3; Medis Medical Imaging Systems, Leiden, the Netherlands) by at least two experienced interventional cardiologists blinded to the clinical data. Arteries were measured at the end-diastolic phase, in which the severity of stenosis appeared maximal. Lesions with a stenosis diameter ≥70% with inducible ischemia were considered clinically significant and defined as culprit lesions to carry out PCI, whereas lesions with mild-to-intermediate stenosis (% diameter stenosis from 30% to 70%) without inducible ischemia at either baseline or follow up were defined as non-culprit lesions. Lesions within 10 mm proximal or distal to the placed stent were considered as the stent segment. Stent diameter and length were analyzed for culprit lesions, and minimum lumen diameter, percentage of stenosis diameter and late loss were analyzed for both culprit and non-culprit lesions. Additionally, we evaluated the occurrence of rapid stenosis progression in non-culprit lesions. RP was defined as follows: ≥10% luminal narrowing progression in lesions with stenosis ≥50%, ≥30% luminal narrowing progression in non-culprit lesion with stenosis <50% or previously normal segment, or progression of stenosis to total occlusion[16,17].

Evaluation of clinical outcome

The clinical outcome was defined as the occurrence of CVE, consisting of cardiovascular death, non-fatal myocardial infarction and ischemia-driven revascularization, including target lesion revascularization (TLR), target vascular revascularization (TVR)

and revascularization for de novo lesions during the 2-year follow-up period. Patients were classified into two groups according to the presence of CVE (CVE [+]) or absence of CVE (CVE [–]).

Outcomes

The primary objective was to evaluate the relationship between glucose fluctuations and overall CVE as well as each individual component. The secondary objective was to evaluate the relationship between glucose fluctuations and angiographical changes in both culprit and non-culprit lesions including RP in non-culprit lesions.

Statistical analysis

All data are presented as the mean ± standard deviation (proportion). The continuous variables were analyzed using Student's *t*-test and the Mann–Whitney test according to normal or non-normal distribution, respectively. The χ^2-test or Fisher's exact test was carried out to compare the proportions of categorical variables. A *P*-value <0.05 was considered statistically significant. All variables with $P < 0.20$ in the initial univariable logistic regression analyses were included in the multivariable logistic regression analysis to identify independent predictors of CVE. A receiver operating characteristic curve analysis was carried out to determine the predictability (sensitivity and specificity) of MAGE for predicting CVE, TLR, TVR and RP, respectively. Simple linear correlations were calculated by determining the Pearson correlation coefficient. Analyses were carried out using commercially available SPSS software (version 25; SPSS Inc, Chicago, IL, USA).

RESULTS

Baseline patient characteristics and clinical outcomes

We enrolled 101 consecutive patients who underwent CGM, index PCI and serial follow-up CAG (Figure 1). Baseline patient characteristics at the timing of index PCI are shown in Table 1. The study population underwent adequate risk management, including lipid-lowering therapy, with 83% receiving statins, 7% receiving ezetimibe, 5% receiving eicosapentaenoic acid, 2% receiving fibrates and 3% using a dietary plan. During the 2 years of follow up, CVE occurred in 25 patients; two had non-fatal myocardial infarction, 17 had TVR and 10 had TLR; the total number is >25 because of overlapping conditions.

Association between CVE and glucose fluctuations

No significant difference was observed between the CVE (+) and CVE (–) groups in terms of baseline characteristics, including lipid and glucose levels (Table 1). However, there were significant differences in MAGE, maximum blood glucose level

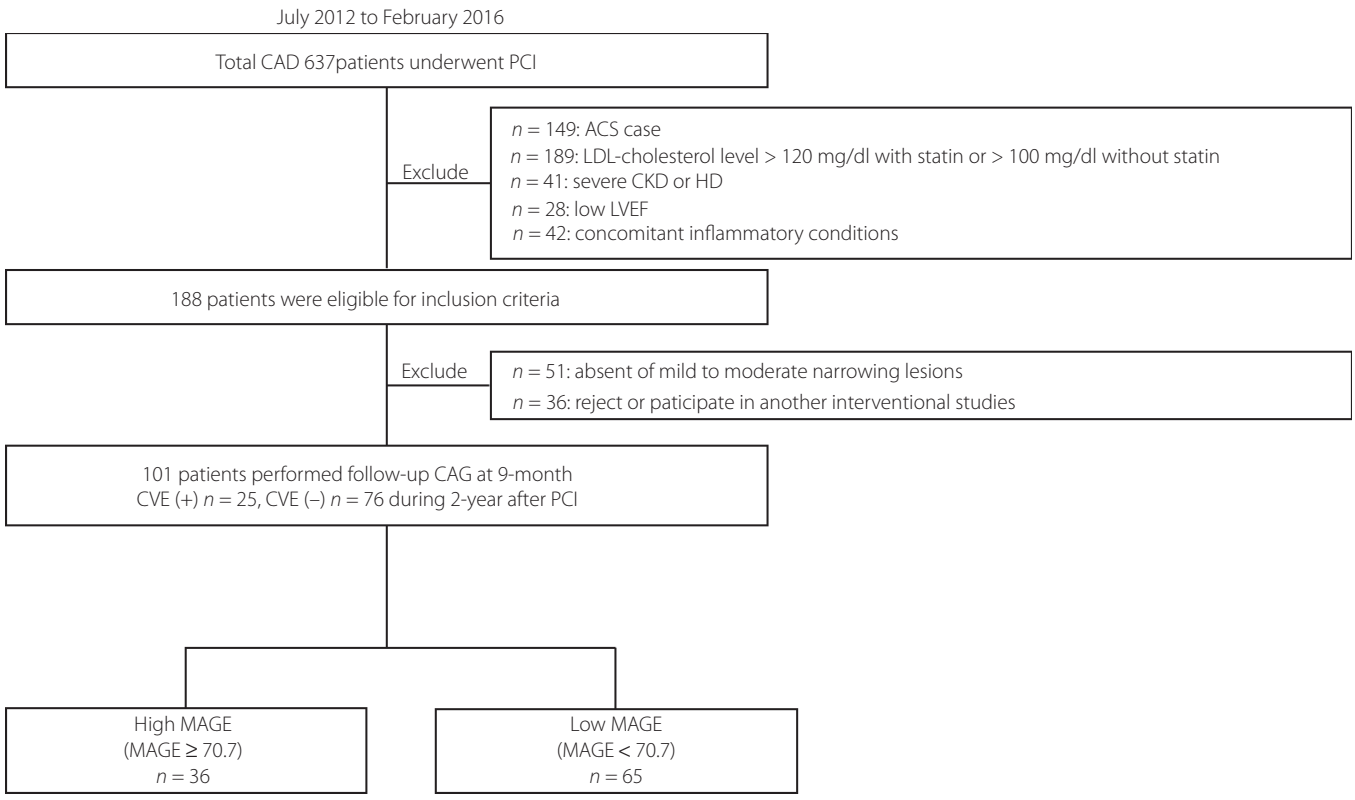

Figure 1 | Study population. A total of 101 consecutive patients were enrolled in this study. ACS, acute coronary syndrome; CAD, coronary artery disease; CAG, coronary angiography; CVE, cardiovascular event; CKD, chronic kidney disease; HD, hemodialysis; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MAGE, mean amplitude of glycemic excursion.

Table 1 | Patient characteristics

	Total *n* = 101	CVE (+) *n* = 25	CVE (-) *n* = 76	*P*
Age (years)	70.8 ± 10.4	72.0 ± 9.6	70.4 ± 10.7	0.5
Male	79 (78)	16 (64)	63 (83)	0.12
BMI (kg/m^2)	24.2 ± 3.2	23.6 ± 2.8	24.4 ± 3.3	0.32
Hypertension	78 (77)	21 (84)	57 (75)	0.14
Dyslipidemia	89 (88)	20 (80)	69 (91)	0.31
DM/IGT/NGT	54 (53)/27 (27)/20 (20)	18 (72)/4 (16)/3 (12)	36 (47)/23 (30)/17 (22)	0.1
Smoking (current/past)	13 (13)/34 (34)	5 (20)/6 (24)	8 (11)/28 (37)	0.32
Prior MI	23 (23)	4 (16)	22 (29)	0.2
Prior PCI	48 (48)	10 (40)	38 (50)	0.39
Prior CABG	2 (1)	0 (0)	2 (3)	0.56
LVEF (%)	59.3 ± 9.5	58.0 ± 11.5	59.7 ± 8.8	0.45
BNP (ng/dL)	73.3 ± 89.7	74.6 ± 74.4	72.9 ± 94.5	0.94
eGFR (mL/min/1.73 m^2)	59.1 ± 16.4	59.1 ± 16.4	59.1 ± 16.5	0.99
HbA1c (%)	6.4 ± 0.9	6.6 ± 0.8	6.3 ± 0.9	0.24
1,5-AG (μg/mL)	15.8 ± 7.2	15.4 ± 6.9	15.9 ± 7.4	0.76
Glycoalbumin (%)	16.2 ± 3.3	16.8 ± 3.5	16.1 ± 3.3	0.41
75-g OGTT				
Fasting PG (mg/dL)	101.3 ± 22.1	102.8 ± 25.8	100.8 ± 20.9	0.69
2-h PG (mg/dL)	205.6 ± 81.6	223.7 ± 78.3	199.9 ± 82.3	0.22
Fasting IRI (μU/mL)	8.3 ± 10.9	10.2 ± 10.2	7.7 ± 6.4	0.32
2-hr IRI (μU/mL)	88.6 ± 87.2	66.1 ± 49.5	95.3 ± 95.0	0.17
HOMA-R	2.0 ± 2.2	2.1 ± 2.2	2.0 ± 2.3	0.87
HOMA-beta	83.3 ± 71.3	68.4 ± 39.8	88.0 ± 78.3	0.24
hs-CRP (mg/dL)	0.17 ± 0.25	0.20 ± 0.23	0.16 ± 0.26	0.48
Total cholesterol (mg/dL)	156.7 ± 28.6	162.4 ± 32.3	154.9 ± 27.0	0.26
LDL cholesterol (mg/dL)	90.7 ± 19.7	92.2 ± 10.2	89.0 ± 18.4	0.46
HDL cholesterol (mg/dL)	45.3 ± 11.5	44.4 ± 12.8	45.6 ± 11.1	0.65
Triglyceride (mg/dL)	129.2 ± 58.3	119.7 ± 40.2	132.3 ± 63.1	0.35
Medications at discharge				
Aspirin	100 (99)	24 (96)	76 (100)	0.76
Thienopyridine	100 (99)	24 (96)	76 (100)	0.76
Statin	84 (83)	19 (76)	65 (86)	0.37
EPA	5 (5)	1 (4)	4 (5)	0.66
Ezetimibe	7 (7)	0 (0)	7 (9)	0.19
Fibrate	2 (2)	1 (4)	1 (1)	0.41
Beta-blocker	52 (51)	12 (48)	40 (53)	0.87
ACE-I/ARB	68 (67)	17 (68)	51 (67)	0.68
Insulin-user	4 (4)	1 (4)	3 (4)	0.67
DPP4-I	49 (49)	14 (56)	35 (46)	0.32
Metformin	16 (16)	6 (24)	10 (13)	0.15
Sulfonylurea	12 (12)	5 (20)	7 (9)	0.12
Alfa-GI	11 (11)	3 (12)	8 (11)	0.52

Values are the mean ± standard deviation or *n* (%). 1,5-AG, 1,5-anhydroglucitol; ACE-I, angiotensin-converting enzyme inhibitor; Alfa-GI, alfa-glucosidase inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass graft; CVE, cardiovascular event; DM, diabetes mellitus; DPP4-I, dipeptidyl peptidase-4 inhibitor; eGFR, estimate glomerular filtration rate; EPA, eicosapentaenoic acid; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-beta, homeostasis model assessment of beta-cells; HOMA-R, homeostasis model assessment of insulin resistance; hs-CRP, highly sensitive C-reactive protein; IGT, impaired glucose tolerance; IRI, immunoreactive insulin; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PCI, percutaneous coronary intervention; PG, plasma glucose.

and time in hyperglycemia between the two groups (Table 2). Univariable analysis showed that MAGE, maximum blood glucose, hypertension and male sex were associated with CVE ($P < 0.2$). Multivariable logistic regression analysis showed that MAGE was an independent predictor of CVE after PCI in this subset (Table 3).

Cut-off MAGE value as a predictor of CVE, TLR, TVR and RP

The optimal threshold of MAGE value was estimated by maximizing the sums of the sensitivity and specificity. The receiver operating characteristic analysis showed that the cut-off MAGE value for the prediction of CVE was 70.7 mg/dL (area under the curve 0.687, 95% confidence interval 0.572–0.802; $P = 0.005$), with sensitivity of 64% and specificity of 75% (Figure 2a). The cut-off MAGE values for predicting TLR, TVR and RP were shown in Figure 2b–d.

Difference of clinical events in high and low MAGE groups

All patients were divided into two groups according to previous described cut-off MAGE values: high MAGE group (MAGE ≥70.7 mg/dL, $n = 36$) and low MAGE group (MAGE <70.7 mg/dL, $n = 65$). Each component of CVE was significantly more prevalent in the high MAGE group (Figure 3).

Association between MAGE and outcome of culprit lesions

We analyzed 133 culprit lesions in 101 patients. The culprit lesion characteristics are shown in Table 4. Almost all culprit lesions were treated with second-generation drug-eluting stent implantation. During follow up, restenosis in the culprit segment occurred for 10 lesions in 10 patients. In-stent late loss in culprit lesions was significantly larger in the high MAGE group rather than in the low MAGE group (0.43 ± 0.53 mm vs 0.09 ± 0.36 mm).

Association between MAGE and angiographical rapid progression of non-culprit lesions

Angiographical findings of 149 non-culprit lesions at the index PCI and follow up are shown in Table 5. The change in the percentage of the stenosis diameter was significantly higher (18.7 ± 15.7% vs 5.6 ± 9.8%; $P < 0.05$; Figure 4a) and in-segment late loss was significantly larger (0.44 ± 0.40 mm vs 0.14 ± 0.27 mm) in the high MAGE group. Additionally, the change in the percentage of the stenosis diameter for all non-culprit lesions was positively correlated with the MAGE value ($r = 0.400$, $P < 0.05$; Figure 4b).

RP in non-culprit lesions occurred in 22 lesions of 20 patients according to the prespecified angiographic criteria: ≥10% luminal narrowing progression in lesions with stenosis ≥50% ($n = 5$), ≥30% luminal narrowing progression in non-culprit lesion with stenosis < 50% ($n = 15$) or ≥30% luminal narrowing progression in non-culprit lesion with previously normal segment ($n = 1$), or progression to total occlusion ($n = 1$). RP occurred significantly more frequently in the high MAGE group than the low MAGE group (33.3% [18/54 lesions] vs 4.2% [4/95 lesions], $P < 0.05$; Figure 4c).

DISCUSSION

It is widely known that patients with diabetes mellitus will experience more CVEs than patients without diabetes mellitus[18]. In addition, diabetes mellitus is strongly associated with a higher rate of TVR due to acute plaque progression in patients

Table 2 | Variables measured by the continuous glucose monitoring system

	Total $n = 101$	CVE (+) $n = 25$	CVE (–) $n = 76$	P
MAGE (mg/dL)	63.5 ± 25.0	76.1 ± 24.8	59.3 ± 23.7	0.003
Mean blood glucose (mg/dL)	132.0 ± 28.1	141.2 ± 27.9	129.0 ± 27.6	0.06
Maximum blood glucose (mg/dL)	217.1 ± 56.9	242.0 ± 63.3	208.9 ± 52.5	0.01
Minimum blood glucose (mg/dL)	77.2 ± 26.3	79.6 ± 26.3	76.4 ± 26.4	0.60
Time to hyperglycemia (%)	33.1 ± 30.0	44.5 ± 29.6	29.2 ± 29.3	0.03
Time to hypoglycemia (%)	2.1 ± 4.4	3.1 ± 6.8	1.7 ± 3.3	0.33

Values are the mean ± standard deviation or *n* (%). CVE, cardiovascular event; MAGE, mean amplitude glycemic excursion.

Table 3 | Univariate and multivariate logistic regression analyses of contributors to cardiovascular events at 2 years after percutaneous coronary intervention

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
MAGE	1.027	1.008–1.047	0.005	1.027	1.008–1.047	0.005
DM	3.536	1.321–9.465	0.012			
Maximum blood glucose	1.010	1.002–1.018	0.015			
Hypertension	2.619	0.707–9.705	0.150			
Male sex	0.480	0.173–1.322	0.159			

CI, confidence interval; DM, diabetes mellitus; MAGE, mean amplitude of glycemic excursion, OR, odds ratio.

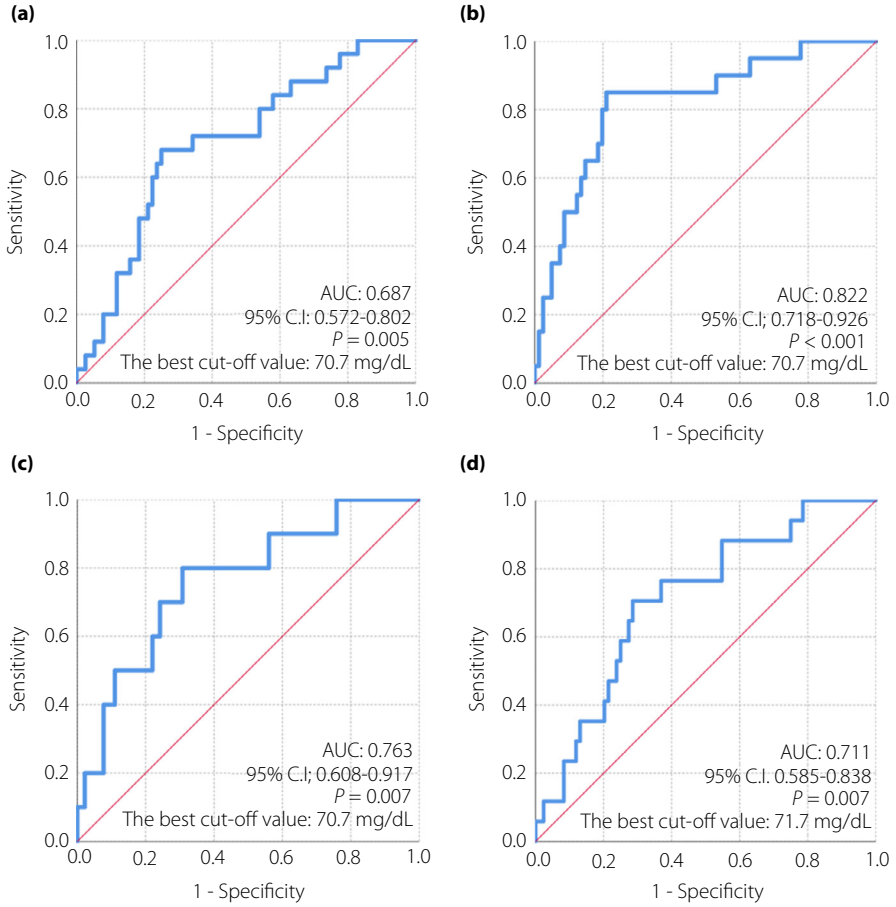

Figure 2 | The cut-off mean amplitude of glycemic excursion (MAGE) value for predicting cardiovascular events including each component. (a) The receiver operating characteristic of MAGE for the prediction of cardiovascular events was constructed. The optimal cut-off value was 70.7 mg/dL (area under the receiver operating characteristic curve [AUC] 0.687, 95% confidence interval [CI] 0.572–0.802; $P = 0.005$). (b) The cut-off MAGE value for predicting target lesion revascularization was also 70.7mg/dL (AUC 0.822, 95% CI 0.718–0.926; $P < 0.001$). (c) The cut-off MAGE value for predicting target vessel revascularization was also 70.7 mg/dL (AUC 0.763, 95% CI 0.608–0.917; $P = 0.007$). (d) The cut-off MAGE value for predicting rapid progression was 71.7 mg/dL (AUC 0.711, 95% CI 0.585–0.838; $P = 0.007$).

who have previously undergone PCI[19]. However, it is unclear which factors have the greatest effects on cardiovascular outcomes of patients with diabetes mellitus. In the present study, we investigated the effects of glucose fluctuations on cardiovascular events after PCI for stable CAD patients undergoing lipid-lowering therapy. The major findings were as follows: (i) MAGE was an independent predictor of 2-year CVE after PCI in lipid-controlled stable CAD patients; (ii) that patients in the high MAGE group (MAGE ≥70.7 mg/dL) more frequently required TLR of culprit lesions and had RP of non-culprit lesions compared with patients in the low MAGE group (MAGE <70.7 mg/dL), and (iii) MAGE was positively correlated with the progression of coronary luminal narrowing of non-culprit lesions. To our best knowledge, this is the first report to show that higher glucose fluctuations are associated with cardiovascular events, even in patients with stable CAD using appropriate lipid management. In a single-center prospective study, Su *et al.*[9] showed that MAGE levels ≥70.2 mg/dL on admission were an independent predictor of an increased risk of 1-year CVE for acute myocardial infarction patients, which was in line with the results of stable CAD in the present study.

Several studies have shown that second-generation drug-eluting stent implantation improves prognosis after PCI compared with the first generation. However, restenosis still occurs and is more frequent among patients with abnormal glucose tolerance[20,21]. Previous reports have suggested that diabetes mellitus is associated with pronounced smooth muscle cell proliferation after vascular injury that mimicked coronary interventions[22]. Furthermore, some studies showed that higher glucose fluctuations have adverse effects on human endothelial cells[23]. Recent studies using animal models showed that higher glucose fluctuations have unfavorable effects on not only the native artery, but also neointimal proliferation after stent

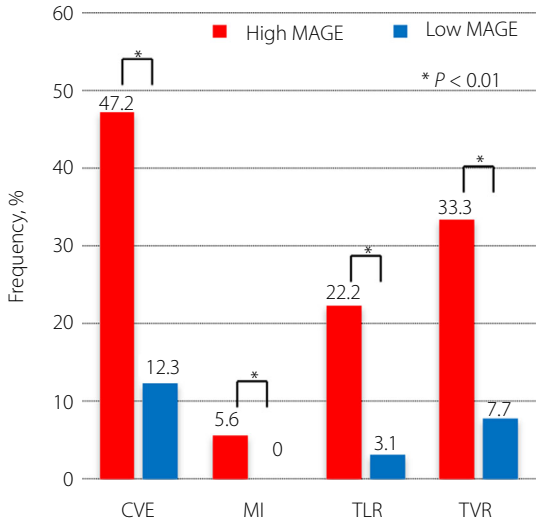

Figure 3 | Glucose fluctuation and clinical prognosis. Incidence of cardiovascular event (CVE), including non-fatal myocardial infarction (MI), target lesion revascularization (TLR) and target vessel revascularization (TVR) in the high and low mean amplitude of glycemic excursion (MAGE) groups.

implantation[24,25]. In our previous study observing vascular healing in response to everolimus-eluting stent implantation using optical coherence tomography, we showed that higher glucose fluctuations were associated with higher rates of uncovered struts and greater variability in neointimal thickness[26]. Therefore, higher glucose fluctuations might have caused abnormal neointimal healing in the stented segment, resulting in increased TLR.

Regarding progression of non-culprit lesions, previous observational studies reported that RP occurs in 28–32% of stable CAD patients[17,27]. In the present study, RP was observed in 22 lesions (14.7%) of a total of 149 non-culprit lesions even in lipid-controlled stable CAD patients. In addition, the present results showed positive relationships between MAGE and progression of non-culprit lesions. Also, Kataoka *et al.*[28] reported that higher MAGE was an independent predictor of RP in non-culprit lesions in ACS patients. Taken together, this evidence shows that higher glucose fluctuations might also influence the plaque progression of non-culprit lesions in either ACS or stable CAD patients. The complexity of coronary artery lesions in cases of high glycemic variability[29] might reflect the effects of the susceptibility to plaque progression in patients with high glucose fluctuation.

Table 4 | Angiographic findings of culprit lesions

	Total		High MAGE		Low MAGE		*P*
	n = 101		(MAGE ≥70.7)		(MAGE <70.7)		
			n = 36		*n* = 65		
No. of diseased vessels							0.80
1	73 (72)		25 (69)		48 (74)		
2	24 (24)		9 (25)		15 (23)		
3	4 (4)		2 (6)		2 (3)		
Culprit lesion location	*n* = 133		*n* = 49		*n* = 84		0.68
LAD	57		22		35		
LCx	32		9		23		
RCA	42		17		25		
LMT	2		1		1		
Culprit lesion PCI variables	*n* = 133		*n* = 49		*n* = 84		0.39
POBA	3		0		3		
BMS	2		1		1		
Second-generation DES	170		63		107		
Stent diameter	3.1 ± 0.4		3.1 ± 0.4		3.1 ± 0.4		0.63
Stent length	22.0 ± 7.3		21.7 ± 7.5		22.1 ± 7.3		0.78
Culprit lesion characteristics	Postoperative	Follow up	Postoperative	Follow up	Postoperative	Follow up	*High MAGE vs low MAGE: *P* < 0.05
Minimum lumen diameter (mm)	2.5 ± 0.4	2.3 ± 0.6	2.51 ± 0.42	2.08 ± 0.63*	2.56 ± 0.44	2.47 ± 0.49*	
Reference lumen diameter (mm)	2.86 ± 0.45	2.83 ± 0.47	2.82 ± 0.43	2.76 ± 0.43	2.88 ± 0.46	2.87 ± 0.49	
Diameter stenosis (%)	11.1 ± 5.4	18.0 ± 13.6	10.9 ± 6.3	25.5 ± 17.8*	11.3 ± 4.9	14.1 ± 8.7*	
In-stent late loss (mm)	–	0.21 ± 0.45	–	0.43 ± 0.53*	–	0.09 ± 0.36*	
ISR in culprit lesion	10/175 (5.7)		8/64 (13)		2/111 (2)		0.005

Values are the mean ± SD, standard deviation or *n* (%). BMS, bare metal stent; DES, drug-eluting stent; ISR, in-stent restenosis; LAD, left anterior descending artery; LCx, left circumflex artery; LMT, left main trunk; MAGE, mean amplitude glycemic excursion; PCI, percutaneous coronary intervention; POBA, plain old balloon angioplasty; RCA, right coronary artery.

Table 5 | Angiographic findings of non-culprit lesions

	Total		High MAGE		Low MAGE		*P*
	n = 101		(MAGE ≥70.7)		(MAGE <70.7)		
			n = 36		*n* = 65		
Non-culprit lesion location	*n* = 149		*n* = 54		*n* = 95		0.64
LAD	39		13		26		
LCx	51		16		35		
RCA	55		23		32		
LMT	4		2		2		
Non-culprit lesion characteristics	Preoperative	Follow up	Preoperative	Follow up	Preoperative	Follow up	*High MAGE vs low MAGE:
Minimum lumen diameter (mm)	1.78 ± 0.50	1.54 ± 0.49	1.87 ± 0.52	1.44 ± 0.57	1.74 ± 0.47	1.59 ± 0.43	*P* < 0.05
Reference lumen diameter (mm)	2.73 ± 0.66	2.77 ± 0.66	2.73 ± 0.65	2.77 ± 0.58	2.74 ± 0.67	2.77 ± 0.70	
Lesion length (mm)	9.33 ± 4.41	10.37 ± 4.54	8.22 ± 4.13*	10.22 ± 3.99	9.96 ± 4.47*	10.46 ± 4.85	
Diameter stenosis (%)	34.4 ± 10.7	44.7 ± 11.8	30.8 ± 11.9*	49.5 ± 13.8*	36.5 ± 9.4*	42.0 ± 9.6*	
In-segment late loss	–	0.24 ± 0.36	–	0.44 ± 0.41*	–	0.14 ± 0.27*	
Rapid progression in non-culprit lesions	22		18 (50)		4 (6)		0.03
≥10% DR in DS ≥50%	5		4 (11)		1 (2)		
≥30% DR in DS <50%	15		12 (33)		3 (5)		
DR ≥30% in normal lesion	1		1 (3)		0 (0)		
Total occlusion in any lesion	1		1 (3)		0 (0)		

Values are the mean ± standard deviation or *n* (%). DR, diameter reduction; DS, diameter stenosis; LAD, left anterior descending artery; LCx, left circumflex artery; LMT, left main trunk; MAGE, mean amplitude glycemic excursion; RCA, right coronary artery.

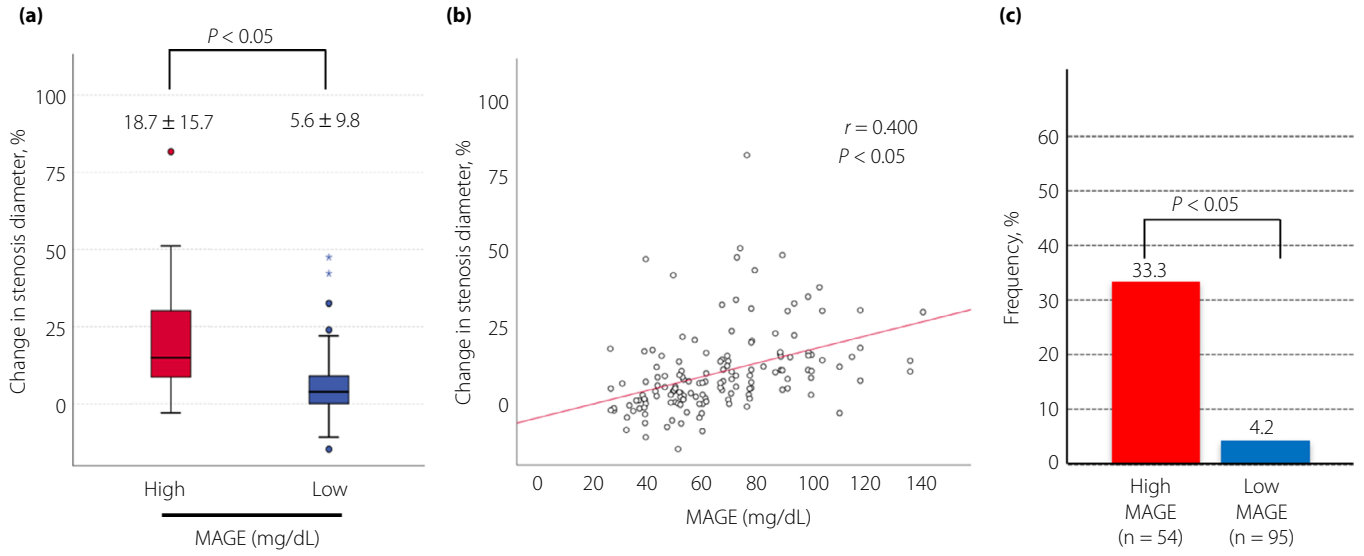

Figure 4 | Glucose fluctuation and luminal narrowing in non-culprit lesions. (a) Changes in percentage of stenosis diameter of non-culprit lesions in the high and low mean amplitude of glycemic excursion (MAGE) groups. (b) The correlation between MAGE and luminal narrowing in all non-culprit lesions. (c) The incidence of rapid progression in non-culprit lesions in the high and low MAGE groups.

It is generally acknowledged that the oxidative stress that accompanies glucose fluctuation and directly promotes atherosclerosis and myocardial apoptosis underlies the increased risk of cardiovascular disease for these patients, as well as animal models[30,31]. Several clinical reports have found that mitigation of MAGE was significantly associated with reduced oxidative stress[32-34]. Recent reports, however, have shown that inflammatory monocytes, which are associated with future cardiovascular events, were significantly correlated with MAGE during the early phase of impaired glucose metabolism[35,36].

Some antidiabetic agents, including alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists, have been shown to improve oxidative stress and glucose fluctuations. Several randomized clinical trials have addressed whether antidiabetic treatments could reduce cardiovascular events. The Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) trial showed that a poor postprandial state accelerates atherosclerosis, even in patients with early impaired glucose tolerance, and that improving the state with acarbose treatment prevented atherosclerosis progression[37]. Another recent study showed that the glucagon-like peptide-1 receptor agonist, liraglutide, reduces the risk of CVE, especially myocardial infarction, compared with a placebo in patients with type 2 diabetes mellitus at high cardiovascular risk[38,39]. Stabilizing glucose fluctuations might have been one of the mechanisms underlying the cardiovascular risk reduction in either impaired glucose tolerance or diabetes mellitus.

After considering these previous findings, we speculated that lowering glucose fluctuations might potentially improve good vascular healing and, consequently, reduce restenosis and repeat revascularization in lesions with RP. More efforts are necessary to optimize secondary prevention of CAD in higher MAGE patients, regardless of the diagnosis of stable CAD or ACS. However, large-scale, randomized clinical trials targeting glucose fluctuations to prevent CVEs have not been carried out. Therefore, further studies investigating whether suppressing glucose fluctuations can protect against cardiovascular events are necessary.

The present study had several limitations. First, this was a small prospective observational study with longitudinal follow up at a single center; therefore, there was a potential risk of patient selection bias. Second, we excluded patients with uncontrolled lipid levels to reduce the influence of the lipid profile. We included only patients who were thought to have well-controlled dyslipidemia. However, recent evidence has shown that lipids should be controlled even more strictly (low-density lipoprotein cholesterol < 70 mg/dL) in CAD patients with diabetes mellitus. Further studies of patients with more strictly controlled dyslipidemia are required to explore the direct effects of glucose fluctuations on cardiovascular outcomes. Third, nonculprit plaques in the same artery as the culprit lesions might have been affected due to procedure during PCI, which might have led to RP.

In conclusion, daily glucose fluctuations might be associated with the progression of both target and non-target lesions after PCI, resulting in increased cardiovascular events, even in stable CAD patients undergoing lipid-lowering therapy. Therefore, daily glucose fluctuations might be a potential target for reducing future cardiovascular events.

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DISCLOSURE

The authors declare no conflict of interest.

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