ORIGINAL ARTICLE

Comparison of the relationship between multiple parameters of glycemic variability and coronary plaque vulnerability assessed by virtual histology–intravascular ultrasound

Natsu Otowa-Suematsu[1], Kazuhiko Sakaguchi[1,2]* (iD), Hisako Komada[1], Tomoaki Nakamura[1], Anna Sou[1], Yushi Hirota[1], Masaru Kuroda[3], Toshiro Shinke[3], Ken-ichi Hirata[3], Wataru Ogawa[1]

Divisions of [1]Diabetes and Endocrinology, [2]General Internal Medicine, and [3]Cardiology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

ABSTRACT

Aims/Introduction: Increased glycemic variability is an important contributing factor to coronary artery disease. Although various parameters of glycemic variability can be derived by continuous glucose monitoring, the clinical relevance of individual parameters has remained unclear. We have now analyzed the relationship of such parameters to coronary plaque vulnerability.

Materials and Methods: The standard deviation of glucose levels (SD glucose), mean amplitude of glycemic excursions (MAGE), continuous overlapping net glycemic action calculated every 1 h (CONGA-1) and mean of daily differences (MODD) were calculated from continuous glucose monitoring data for 53 patients hospitalized for percutaneous coronary intervention. The relationship of these parameters to the percentage necrotic core of total plaque volume (%NC) as assessed by virtual histology–intravascular ultrasound (a predictor of coronary plaque rupture) was evaluated.

Results: All parameters of glycemic variability were significantly correlated with %NC, with correlation coefficients of 0.593, 0.626, 0.318, and 0.388 for log(SD glucose), log (MAGE), CONGA-1 and log(MODD), respectively. Simple linear regression analysis showed that the coefficients of determination for %NC and either log(SD glucose; 0.352) or log (MAGE; 0.392) were greater than those for %NC and either CONGA-1 (0.101) or log(MODD; 0.151), whereas the residual sums of squares for the former relationships (1045.1 and 979.5, respectively) were smaller than those for the latter (1449.3 and 1369.6, respectively).

Conclusions: The present data suggest that SD glucose and MAGE are more highly correlated with coronary plaque vulnerability than are CONGA-1 and MODD, and are thus likely better predictors of coronary artery disease.

INTRODUCTION

Glucose intolerance, including impaired glucose tolerance (IGT) and diabetes mellitus, is an important risk factor for coronary artery disease (CAD)[1,2]. In these metabolic conditions, not only the increase in blood glucose concentration (hyperglycemia), but also fluctuation in this parameter (glycemic variability) likely contributes to the pathogenesis of CAD. Evidence suggests that glycemic variability is highly correlated with

predictive factors for or the development of CAD in a manner independent of conventional markers of hyperglycemia, such as the level of glycosylated hemoglobin[3,4].

Continuous glucose monitoring (CGM) allows the determination of various parameters related to glycemic variability[5,6]. The standard deviation of glucose levels (SD glucose) and mean amplitude of glycemic excursions (MAGE) are widely used indexes of intraday glycemic variability[5,6], and have been shown to correlate with various predictive factors for CAD[7–10]. The mean of daily differences (MODD) is an index of interday

glycemic variability and was found to be correlated with a circulating marker of oxidative stress[11], an important pathogenic factor for CAD[12]. Continuous overlapping net glycemic action calculated every 1 h (CONGA-1) was introduced relatively recently as an objective and accurate index of intraday glycemic variability[13], but its relationship to CAD has remained unknown.

Histological characteristic of atherosclerotic plaques is a strong determinant of rupture of the lesions[14], a key step in coronary events. Evidence suggests that plaque components assessed by virtual histology–intravascular ultrasound (VH-IVUS) are useful markers of plaque vulnerability and strong predictors of coronary events[15]; parameters of plaque vulnerability assessed by VH-IVUS have been shown to correlate with MAGE[16,17].

To provide further insight into the connection between glycemic variability and CAD, we measured various indexes of glycemic variability, including SD glucose, MAGE, CONGA-1 and MODD, in patients with CAD and then analyzed the relationship of these parameters of glycemic variability to plaque vulnerability assessed by VH-IVUS.

METHODS

Study participants

The present retrospective observational study was approved by the ethics committee of Kobe University Graduate School of Medicine, conformed to the provisions of the 1995 Declaration of Helsinki and was registered with the University Hospital Medical Information Network (UMIN000018326). A total of 336 consecutive patients who underwent percutaneous coronary intervention (PCI) for evaluation of potential CAD on admission at Kobe University Hospital, Kobe, Japan, between June 2012 and May 2014 was screened according to the following inclusion and exclusion criteria. Inclusion criteria included:

(i) age of 20–80 years; (ii) well-controlled serum cholesterol level (low-density lipoprotein cholesterol level of <120 mg/dL under statin administration or <100 mg/dL under other treatment for dyslipidemia including lifestyle intervention); and (iii) analysis with a 75-g oral glucose tolerance test (OGTT) and CGM during admission. Exclusion criteria included: (i) PCI for acute coronary syndrome; (ii) unsuitable anatomy for VH-IVUS; (iii) poor imaging by VH-IVUS; (vi) hemodialysis, inflammatory disease, shock, low cardiac output or concurrent malignant disease; and (iv) consecutive 48-h data for CGM not available. A total of 53 individuals who met the criteria were studied.

CGM and OGTT-based clinical parameters

During admission, all patients received a standard diet (25–30 kcal/kg of ideal body mass, consisting of 50–60% carbohydrate, 20–25% fat and 15–20% protein per day) in three equal portions at 07.00, 12.00 and 18.00 h. Ideal body mass was defined as a body mass index of 22 kg/m². A 75-g OGTT, as well as CGM with the use of an iPro2 CGM system (Medtronic, Northridge, CA, USA) for at least three consecutive days, were carried out within 7 days before PCI, and data for the second and third day of CGM were analyzed. Various parameters of glycemic variability were calculated with the use of EasyGV software[18] (available at www.easygv.co.uk). The calculating formulae of the parameters are shown in Table 1. An OGTT-based disposition index (oral DI) was calculated as the product of the Matsuda Index and the ratio of the area under the insulin curve to the area under the glucose curve from 0 to 120 min ($AUC_{Ins/glu120}$), as described previously[19].

VH-IVUS

During PCI, VH-IVUS was carried out with the use of an Eagle Eye Platinum 3.5-Fr 20-MHz catheter (Volcano, Rancho

Table 1 | Calculating formula of the various parameters of glycemic variability

Name	Formula	
SD	$SD = \sqrt{\dfrac{\sum (x_i - \bar{x})^2}{n-1}}$	
MAGE	$MAGE = \sum \dfrac{\lambda}{x}$ if $\lambda > v$	λ = blood glucose changes from peak to nadir x = number of valid observations v = 1 SD of mean glucose for a 24-h period
MODD	$MODD = \dfrac{\sum_{t=t_1}^{t_k} |G_t - G_{t-1440}|}{k}$	k = number of observations with an observation 24 h ago G = glucose measured t = time
CONGA-1	$CONGA = \sqrt{\dfrac{\sum_{t=t_1}^{t_k} (D - \bar{D})^2}{k-1}}$ $\bar{D} = \dfrac{\sum_{t=t_1}^{t_k} D_t}{k}$ $D^t = G^t - G^{t-m}$	k = number of observations where there is an observation 1 × 60 min ago m = 1 × 60 G = glucose measured

CONGA-1, continuous overlapping net glycemic action calculated every 1 h; MAGE, mean amplitude of glycemic excursions; MODD, mean of daily differences; SD, standard deviation.
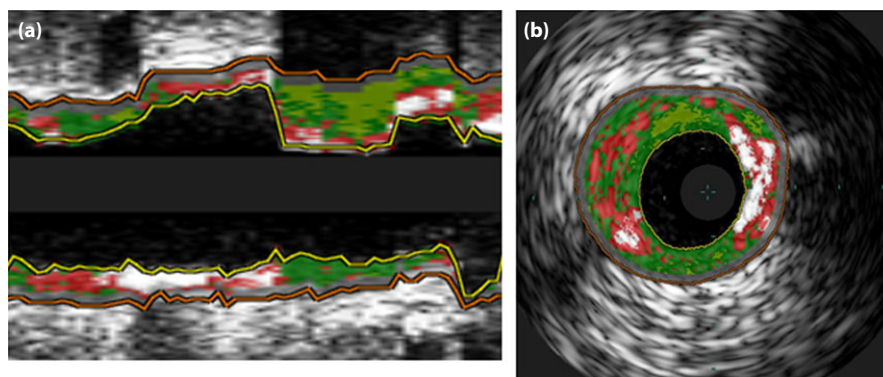
Figure 1 | A representative virtual histology–intravascular ultrasound image of the coronary plaque in (a) longitudinal and (b) cross-sectional views. Yellow and orange lines indicate the lumen and the media-adventitia interface, respectively. Plaque components are grouped into four tissue types and shown as different color pixels: fibrous (dark green), fibrofatty (light green), dense-calcium (white) and necrotic core (red). The percentage of necrotic core in a total plaque volume was analyzed.

Cordova, CA, USA), as described previously[16]. A representative image of coronary plaque in the VH-IVUS is shown in Figure 1. A total of 122 plaques was detected, with an average plaque number of 2.3 per patient. We analyzed the relationship between indexes of glycemic variability and the percentage necrotic core of total plaque volume (%NC), a widely used parameter of plaque vulnerability[15]. For patients with multiple plaques, we calculated an average value of %NC.

Data are presented as mean ± SD. Statistical analysis was carried out with the use of SPSS 22.0 software (SPSS, Chicago, IL, USA). The relationship between two variables was assessed with Pearson's correlation coefficient. Data were compared among groups by one-way ANOVA followed by the Tukey–Kramer method. We applied natural logarithmic transformation for data not normally distributed. Simple linear regression analysis was applied to assess the influence of parameters of glycemic variability on %NC. A *P*-value <0.05 was considered statistically significant.

RESULTS

Among the 53 studied participants, eight, 16, and 29 individuals were categorized as having normal glucose tolerance (NGT), IGT and diabetes mellitus, respectively, according to the results of the OGTT. The characteristics of the participants are provided in Table 2.

The mean glucose level, daily duration of hyperglycemia (>140 mg/dL) and CONGA-1 of the diabetes mellitus group were greater than those of the IGT and NGT groups, whereas SD glucose, MAGE and MODD did not differ significantly among the three groups (Table 3).

Although %NC did not differ among the three categories of glucose tolerance (Table 2), and was not significantly correlated with conventional parameters of glycemic control (glycosylated hemoglobin $r = 0.221$, $P = 0.112$; glycated albumin $r = 0.270$, $P = 0.061$; 1,5-anhydroglucitol $r = -0.253$, $P = 0.076$), it was significantly correlated with all the parameters of glycemic

variability tested (Figure 2). The oral disposition index, which reflects the capacity for glucose disposal[19], decreased with progression from NGT to IGT to diabetes mellitus (Table 2), but it was also not correlated with %NC ($r = -0.185$, $P = 0.202$). The correlation coefficient for simple correlation analysis of %NC was highest for log(MAGE; $r = 0.626$) and log(SD glucose; $r = 0.593$; Figure 2).

Simple linear regression analysis of %NC showed that the coefficients of determination for log(SD glucose) and log(MAGE) were higher, and the residual sums of squares for these two parameters were lower, compared with those for mean glucose level, CONGA-1 and log(MODD; Table 4).

Among CGM-derived parameters, strong correlations were apparent between log(SD glucose) and log(MAGE; $r = 0.902$, $P < 0.001$), and between CONGA-1 and mean glucose level ($r = 0.984$, $P < 0.001$).

DISCUSSION

Although previous reports have shown that MAGE was correlated with coronary plaque vulnerability[16,17], the current study is the first to evaluate the correlation between multiple parameters of glycemic variability and coronary plaque vulnerability, as well as to compare the clinical relevance of individual parameters of glycemic variability. We have here shown that coronary plaque vulnerability as evaluated by VH-IVUS is significantly correlated with all the parameters of glycemic variability we tested, which include MAGE, SD glucose, CONGA-1 and MODD. Both simple correlation and simple linear regression analyses showed that MAGE and SD glucose were the most highly and second most highly correlated, respectively, with coronary plaque vulnerability, suggesting that these parameters are superior to the other two parameters of glycemic variability for prediction of coronary plaque vulnerability.

Although the potential importance of glycemic variability in the development of CAD has been recognized, information on differences in the pathophysiological impact of various

Table 2 | Characteristics of the study participants according to glucose tolerance

Characteristic	All	NGT	IGT	DM
n	53	8	16	29
Male (%)	88.7	87.5	100	82.8
Age (years)	70.2 ± 10.0	68.0 ± 11.8	72.4 ± 10.4	69.1 ± 9.1
BMI (kg/m^2)	24.0 ± 3.2	23.7 ± 3.6	23.2 ± 2.2	24.8 ± 2.7
sBP (mmHg)	121.0 ± 11.6	118.0 ± 8.6	122.8 ± 10.5	121.2 ± 12.9
dBP (mmHg)	62.4 ± 6.8	62.3 ± 6.0	63.2 ± 6.9	62.5 ± 6.4
HbA$_{1c}$ (%)	6.37 ± 0.94	5.73 ± 0.33	5.77 ± 0.33	6.83 ± 1.09*,**
FPG (mg/dL)	104.6 ± 22.8	88.8 ± 7.9	91.8 ± 10.1	116.4 ± 25.9*,**
F-IRI (μg/mL)	7.63 ± 6.22	8.50 ± 4.89	6.40 ± 3.53	8.86 ± 7.88
HOMA-IR	2.13 ± 2.58	1.86 ± 1.03	1.45 ± 0.76	2.81 ± 3.60
HOMA-β	76.5 ± 56.8	126.7 ± 89.9	93.2 ± 68.0	65.9 ± 40.2
Insulinogenic index	0.54 ± 0.54	1.16 ± 0.91	0.79 ± 0.59	0.28 ± 0.22*
AUC$_{Ins/glu120}$	0.36 ± 0.29	0.59 ± 0.31	0.46 ± 0.30	0.30 ± 0.30
Matsuda Index	4.82 ± 3.00	4.87 ± 3.73	5.00 ± 2.73	3.96 ± 2.20
Oral DI	1.34 ± 0.80	2.09 ± 0.51	1.75 ± 0.55*	0.83 ± 0.48*,**
LDL-C (mg/dL)	88.1 ± 19.5	97.5 ± 12.1	78.8 ± 20.1	90.0 ± 22.7
HDL-C (mg/dL)	44.0 ± 11.6	46.5 ± 15.0	46.2 ± 14.0	42.4 ± 9.4
TG (mg/dL)	135.6 ± 71.2	136.8 ± 43.1	95.4 ± 33.0	156.0 ± 77.2
%NC	19.4 ± 5.6	14.7 ± 3.9	15.3 ± 3.5	20.3 ± 5.0
Medication on admission, n (%)				
Aspirin	43 (81.1)	4 (50.0)	14 (87.5)	25 (86.2)
Thienopyridine	24 (45.3)	3 (37.5)	6 (37.5)	15 (51.7)
Statin	41 (77.4)	6 (75.0)	11 (68.8)	24 (82.8)
ACE-I/ARB	33 (62.3)	3 (37.5)	10 (62.5)	20 (69.0)
Beta-blocker	24 (45.3)	3 (37.5)	7 (43.8)	14 (48.3)
Insulin	1 (1.9)			1(3.5)
GLP-1 RA	0 (0)			0 (0)
DPP-4I	13 (24.5)			13 (44.8)
Sulfonylurea	9 (17.0)			9 (31.0)
Metformin	3 (5.7)			3 (10.3)
SGLT2-I	0 (0)			0 (0)
α-Glucosidase inhibitor	3 (5.7)			3 (10.3)
Glinide	0 (0)			0 (0)
Pioglitazone	0 (0)			0 (0)

Data are means ± standard deviation or n (%). *P < 0.05 vs normal glucose tolerance (NGT), **P < 0.05 vs impaired glucose tolerance (IGT). Statistical comparison was performed by one-way ANOVA and followed by the Tukey–Kramer method. ACE-I, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; AUC$_{Ins/glu120}$, the ratio of the area under the insulin curve to the area under the glucose curve from 0 to 120 min of the oral glucose tolerance test; BMI, body mass index; dBP, diastolic blood pressurez; DI, disposition index; DM, diabetes mellitus; DPP4-I, dipeptidyl peptidase-4 inhibitor; F-IRI, fasting serum immunoreactive insulin concentration; FPG, fasting plasma glucose concentration; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA$_{1c}$, glycosylated hemoglobin; HDL-C, high density lipoprotein cholesterol; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol; sBP, systolic blood pressure; SGLT2-I, sodium–glucose cotransporter-2 inhibitor; TG, triglyceride.

parameters of glycemic variability has been limited. Two previous studies found that MAGE was more highly correlated with markers of endothelial dysfunction (flow-mediated dilation and reactive hyperemia index, respectively) than were other parameters of glycemic variability including MODD, largest amplitude of glycemic excursions, and mean postprandial glycemic excursions[8] or SD glucose and mean postprandial glycemic excursions[9]. The present data now provide further support for the clinical utility of MAGE in the prediction of CAD, which was suggested by the analysis of surrogates of this condition.

Carotid intima thickness was also found to be more highly correlated with MAGE than with largest amplitude of glycemic excursions[10].

The mechanism underlying the stronger correlation of plaque vulnerability with MAGE and SD glucose than with CONGA-1 and MODD remains unknown. CONGA-1, a parameter of intraday glycemic variability, as are MAGE and SD glucose, is calculated as the SD of the difference in glucose level between each time-point and 1 h before the time-point. This parameter thus reflects variability of glycemia over a short period (1 h). It

Table 3 | Parameters of glycemic variability for the study participants according to glucose tolerance

Parameter	All	NGT	IGT	DM
Mean glucose level (mg/dL)	133.6 ± 27.3	108.0 ± 7.5	117.9 ± 12.5	147.8 ± 27.0*,**
SD glucose (mg/dL)	27.1 ± 1.6	18.7 ± 6.3	22.0 ± 5.1	30.1 ± 13.0
MAGE (mg/dL)	67.0 ± 38.8	45.2 ± 17.9	45.5 ± 12.2	73.5 ± 44.3
CONGA-1 (mg/dL)	119.6 ± 26.7	95.0 ± 6.5	105.5 ± 13.3	132.9 ± 27.3*,**
MODD (mg/dL)	21.7 ± 9.3	15.5 ± 2.7	16.3 ± 5.6	23.5 ± 9.6
Daily duration of hyperglycemia (h)	16.6 ± 14.3	2.0 ± 2.3	7.8 ± 6.1	24.3 ± 15.5*,**
Daily duration of hypoglycemia (h)	1.00 ± 2.12	0.88 ± 0.77	1.09 ± 1.93	0.65 ± 1.78

Data are means ± standard deviation. Hyperglycemia and hypoglycemia were defined as detected glucose values of >140 and <70 mg/dL, respectively. *$P < 0.05$ vs normal glucose tolerance (NGT), **$P < 0.05$ vs impaired glucose tolerance (IGT). Statistical comparison was carried out by one-way ANOVA and followed by the Tukey–Kramer method. CONGA-1, continuous overlapping net glycemic action calculated every 1 h; DM, diabetes mellitus; MAGE, mean amplitude of glycemic excursions; MODD, mean of daily differences; SD, standard deviation.
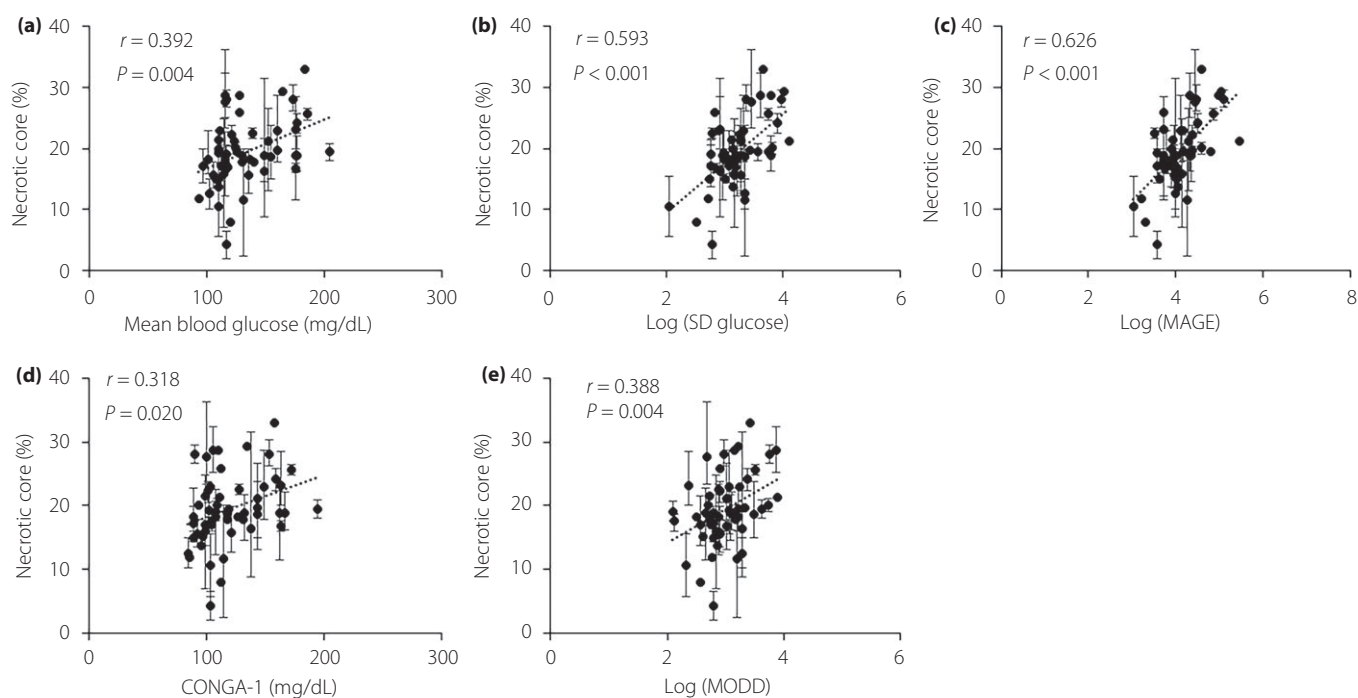

Figure 2 | Correlation analysis for percentage of necrotic core and (a) mean blood glucose level, (b) log(standard deviation of glucose levels), (c) log(mean amplitude of glycemic excursions), (d) continuous overlapping net glycemic action calculated every 1 h (e) and log(mean of daily differences). Data are mean ± standard deviation for percentage of necrotic core of each participant.

is possible that large swings in glycemia over a longer time period, such as those detected by MAGE or SD glucose, exert a greater pathological influence than those over a short period. Although evidence suggests that interday glycemic variability is correlated with CAD[20], such variability might have a smaller impact than large swings in glycemia during a day, given the weaker correlation of %NC with MODD than with MAGE or SD glucose.

We evaluated glycemic variability in hospitalized patients who were provided meals with a constant nutritional balance at fixed times, which should have minimized the influence of day-to-day variability in food intake. Although glycemic variability in such settings might differ from that in daily life, multiple parameters for glycemic variability were significantly correlated with coronary plaque vulnerability. It is thus possible that glycemic variability assessed by CGM reflects an essential pathophysiological feature related to the development of atherosclerotic plaques in patients with CAD. The relatively small number of participants and its retrospective observational design were limitations of the present study.

In conclusion, the present data suggest that MAGE and SD glucose are superior to CONGA-1 and MODD for prediction

Table 4 | Simple linear regression analysis for percentage of necrotic core and parameters of glycemic variability

Parameter	R^2	Residual sum of squares
Mean glucose level	0.154	1364.4
Log(SD glucose)	0.352	1045.1
Log(MAGE)	0.392	979.5
CONGA-1	0.101	1449.3
Log(MODD)	0.151	1369.6

R^2, coefficient of determination. CONGA-1, continuous overlapping net glycemic action calculated every 1 h; MAGE, mean amplitude of glycemic excursions; MODD, mean of daily differences; SD, standard deviation.

of coronary plaque vulnerability. A prospective study with a larger number of participants to assess the impact of each parameter of glycemic variability in each category of glucose tolerance (NGT, IGT or diabetes mellitus) is warranted to provide further insight into the pathology of glycemic variability.

DISCLOSURE
The authors declare no conflict of interest.

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