Associations among glycemic excursions, glycated hemoglobin and high-sensitivity C-reactive protein in patients with poorly controlled type 2 diabetes mellitus

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Abstract. The aim of the present study was to explore the associations among glycemic excursions, glycated hemoglobin (HbA1c) and high-sensitivity C-reactive protein (hs-CRP) in patients with poorly controlled type 2 diabetes mellitus (T2DM) using a continuous glucose monitoring system (CGMS). Sixty-three patients with T2DM whose HbA1c levels were >7% wore a CGMS device for 72 h. According to their HbA1c levels, patients were divided into three groups as follows: Group A (HbA1c ≤9.32%), group B (9.32%< HbA1c ≤11.76%) and group C (HbA1c >11.76%). Patients were also divided into two groups according to the mean amplitude of glycemic excursions (MAGE) as follows: Low glycemic excursion group (MAGE, <3.9 mmol/l) and high glycemic excursion group (MAGE, ≥3.9 mmol/l). Clinical data and the hs-CRP levels in different groups were compared. No significant difference was observed in the MAGE among groups A, B and C (P>0.05). The level of hs-CRP was significantly higher in group C compared with that in groups A and B, and in group B compared with that in group A (P<0.05). Multivariate stepwise regression analysis indicated that HbA1c correlated with hs-CRP (P<0.05). MAGE and HbA1c were independent indices for the assessment of glycemic control. In addition, HbA1c had a considerable effect on the serum hs-CRP level.

Introduction

The worldwide prevalence of diabetes (DM) is increasing; the prevalence in adults ≥20 years of age was 9.7% in China at the end of 2008 (1). In 2010, the China Noncommunicable Disease Surveillance Group estimated that the overall prevalence of DM in the Chinese adult population was 11.6%. In addition, the prevalence of preDM was estimated to be 50.1% (2). These results indicate that DM has become a public health problem in China. According to a report by the chronic complications investigation team of the Diabetes Society of the Chinese Medical Association, the prevalence of type 2 (T2)DM-related complications among the hospitalized patients in third-grade class-A hospitals included 12.6% cerebrovascular diseases, 17.1% cardiovascular diseases and 5.2% lower extremity diseases. The medical expenses required to control cardiovascular and cerebrovascular diseases accounted for the major proportion of the total medical expenses for DM (3). The increase in the size of the diabetic population and the duration of the disease indicate that the complications may constitute a considerable challenge for the Chinese health system in the next two decades.

The 6.5-year follow-up of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study suggested that intensive treatment was associated with reduced glycated hemoglobin (HbA1c) levels, lower intima-media thickness and coronary calcification score and a reduced incidence of clinical cardiovascular events, stroke and cardiovascular death (4). In addition, the conclusion of a further study with 13-14 years of follow-up was that intensive treatment markedly reduced the risks of peripheral (64%) and cardiovascular (45%) autonomic neuropathy in patients with DM (5). The 10-year follow-up of the UK Prospective Diabetes study demonstrated that the microvascular complications of the patients that received intensive treatment were decreased by 24%, and the risk of myocardial infarction by 15% compared with those receiving conventional dietary therapy (6). Clinical studies have demonstrated that the incidence of diabetic complications was markedly reduced when the HbA1c level was reduced by 1% (7,8), suggesting that it is necessary for blood glucose (BG) levels to decrease for HbA1c levels to recover; however, the closer the BG level is to normal values, the higher the risk of hypoglycemia is (9). Furthermore, hypoglycemia results in larger glycemic excursions, and continuous hyperglycemia is considered to be associated with an increased occurrence and development of diabetic complications (10,11). A previous study found that glycemic excursions can induce oxidative stress (12) and cause vascular endothelial cell injury. In addition, a close association has been found between glycemic excursions and diabetic complications (13-15); however, the effect of glycemic excursions and continuous hyperglycemia on a patient with diabetic complications remains unclear.

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Damage caused by low levels of systemic inflammation is an important factor in the pathogenesis of DM and its associated complications (16). High-sensitivity C-reactive protein (hs-CRP) is an important inflammatory factor; it is deposited in local atherosclerotic lesions, thus inducing endothelial cells to express interleukin-6 and other inflammatory cytokines, and is directly involved in the formation and rupture of plaques, as well as thrombosis (17). Previous studies have suggested that serum hs-CRP levels are higher in patients with T2DM with complications than in patients without (18,19). A case control study of patients with DM and normal lipid profiles suggested that hs-CRP was an independent predictor of cardiovascular risk in patients with T2DM (19) and closely associated with diabetic complications. Glucose monitoring is the most important step in the treatment of DM. Continuous glucose monitoring systems (CGMSs) generate dynamic curves for glycemic variability. In the present study, a CGMS was used in order to explore the correlation between glycemic excursion and HbA1c and hs-CRP levels in patients with poorly controlled T2DM.

Materials and methods

Patients. Sixty-three patients with T2DM (34 males, 29 females) were admitted to the First Affiliated Hospital of the Dalian Medical University (Dalian, China) between June 2012 and February 2013. The present study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Dalian Medical University. Written informed consent was obtained from all participants.

Inclusion criteria. Included in the present study were patients aged 18-75 years who had been diagnosed with T2DM (based on the World Health Organization diagnostic criteria for DM) and their HbA1c level was >7%.

Exclusion criteria. Excluded from the study were: Patients with type 1 (T1), gestational or any other special type of DM; patients with a history of DM ketoacidosis or hypoglycemic coma in the last month prior to the study, patients with any clinical evidence of cardiac, renal or liver dysfunctions [glomerular filtration rate, <60 ml/min/1.73 m^2; alanine transaminase (ALT), >100 U/l)] or any hemoglobinopathy within the preceding 3 months; patients who had used non-steroidal anti-inflammatory drugs in the month prior to the study; patients with a history of malignant tumor, severe infection, surgery, other stress-inducing conditions such as infection and trauma, and patients with a history of drug or alcohol abuse.

Definition of microvascular complications. Ophthalmologists examined whether patients had retinopathy by ophthalmoscopy; nephropathy was diagnosed based on the ratio of urinary albumin excretion to Cr levels being >30 mg/g. A nerve conduction velocity test was used to diagnose peripheral neuropathy. Cerebral infarction was diagnosed by a computed tomography scan of the head, coronary heart disease by coronary angiography, and arteriosclerosis obliterans of the lower extremity by Color Doppler ultrasound.

One patient had old inferior wall myocardial infarction, 1 patient old anterior wall myocardial infarction and 1 patient arteriosclerosis obliterans of the right lower extremity.

Laboratory parameters. Age, weight, height and blood pressure were recorded in order to calculate body mass index (BMI) values. Blood samples were collected in the morning before breakfast (8:00-11:00 a.m.), following an overnight fast of 8-12 h. Fast plasma glucose (FPG), HbA1c, total cholesterol (TC), total triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), ALT, aspartate aminotransferase (AST), uric acid (UA), blood urea nitrogen (BUN) and creatinine (Cre) were measured using an automatic biochemistry analyzer. Levels of hs-CRP were measured by immunoturbidimetry.

Groups. According to different HbA1c levels, patients were divided into 3 groups as follows: Group A (HbA1c ≤9.32%), group B (9.32% <HbA1c ≤11.76%), group C (HbA1c >11.76%). In addition, according to their mean amplitude of glycemic excursions (MAGE), patients were divided into two groups as follows: Low glycemic excursion group (MAGE, <3.9 mmol/l) and high glycemic excursion group (MAGE, ≥3.9 mmol/l) (20).

CGMS use and parameters. A CGMS (MMT-7102; Medtronic, Inc. Minneapolis, MN, USA) was used by the patients on day 2 following admission to hospital. The patients were given a glucometer (ACCU-CHEK performa; Roche Diagnostics GmbH, Mannheim, Germany), which used the glucose oxidase principle to measure capillary BG, and were asked to measure their BG prior to and following meals and snacks 7 times a day, including before and 2 h after meals and before sleep, and record the values in the CGMS for better calibration. These glucose concentrations (measured by the CGMS and glucometer) were downloaded after 72 h and interpreted using Solutions MMT-7310, version 3.0C (Medtronic, Inc.).

Related parameters included 24 h mean BG (MBG), standard deviation of BG (SDBG), MAGE and absolute mean of daily differences (MODD).

Statistical analysis. Statistical analysis was performed using SPSS 20.0 software (IBM Corp, Armonk, NY, USA) and all results are presented as mean ± standard deviation. Normally distributed values were analyzed using analysis of variance. Qualitative variables were compared using the χ^2 test. Comparisons of quantitative variables between two groups were performed using Student's t-test. Pearson's correlation analysis was used to determine the correlation between two indices. Multivariate linear regression analysis was used to identify variables independently associated with HbA1c in the two groups. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Differences among groups of patients with different HbAlc levels. No significant differences were observed in the age, disease course, BMI, FPG, systolic blood pressure (SBP), diastolic blood pressure (DBP), TC, TG, LDL-C, HDL-C, ALT, AST, BUN, Cre, UA, MAGE, SDBG and MODD among the groups A, B and C ($P>0.05$). The hs-CRP and 24 h MBG levels were significantly higher in group C compared with those in groups A and B, and in group B compared with those in group A ($P<0.05$). Thus, it appeared that as the HbA1c levels increased, the hs-CRP and

Table I. Clinical data from patients with T2DM of different HbA1c levels.

Variables	Group A (n=21)	Group B (n=21)	Group C (n=21)	P-value
Age (years)	54.27±9.91	55.68±10.35	48.66±11.73	0.398
Male gender, n (%)	10 (47.61)	14 (66.67)	12 (57.14)	
Course of disease (years)	10.31±4.13	7.05±3.19	5.84±2.92	0.274
BMI (kg/m^2)	26.10±2.21	26.29±3.72	26.51±4.16	0.971
SBP (mmHg)	136.79±26.67	137.55±28.21	141.34±27.30	0.652
DBP (mmHg)	79.25±9.32	82.74±9.19	83.66±9.87	0.648
FPG (mmol/l)	10.62±0.83	10.93±0.81	11.10±0.80	0.052
TC (mg/dl)	157.45±45.78	160.10±37.79	161.51±54.72	0.492
TG (mg/dl)	231.36±51.26	246.45±69.04	260.69±62.48	0.171
LDL-C (mg/dl)	101.68±32.57	100.42±18.58	114.81±21.72	0.357
HDL-C (mg/dl)	49.51±10.21	48.68±9.98	52.63±10.04	0.682
ALT (U/l)	35.88±9.80	38.47±9.46	40.35±9.91	0.167
AST (U/l)	36.11±9.19	38.32±8.16	39.29±7.55	0.340
BUN (mmol/l)	5.92±1.79	6.17±1.43	6.16±1.77	0.811
Cre (μmol/l)	50.29±10.11	55.73±10.21	54.39±10.64	0.665
UA (μmol/l)	312.40±80.58	331.54±79.60	368.19±85.07	0.665
24h MBG (mmol/l)	9.81±0.63	12.19±0.61[a]	14.66±0.78[b,c]	0.024
MAGE (mmol/l)	4.75±1.73	5.32±1.61	5.80±1.58	0.263
SDBG (mmol/l)	2.25±0.69	2.49±0.82	2.66±0.71	0.135
MODD (mmol/l)	2.98±0.37	3.09±0.34	3.26±0.53	0.688
hs-CRP (mg/l)	2.46±0.66	4.93±0.32[a]	7.26±0.65[b,c]	0.012
Macrovascular complications, cases (%)	7 (33.33)	9 (42.85)	9 (42.85)	
Microvascular complications, cases (%)	8 (18.64)	6 (13.55)	5 (11.86)	

Values presented are mean ± standard deviation, unless otherwise specified. HbA1c, glycated hemoglobin; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, total triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cre, creatinine; UA, uric acid; MBG, mean blood glucose; MAGE, mean amplitude of glycemic excursion; SDBG, standard deviation of blood glucose; MODD, means of daily differences; hs-CRP, high-sensitivity C-reaction protein. [a]P<0.05 and [b]P<0.05 vs. group A; [c]P<0.05, vs. group B.

24 h MBG levels also increased. No significant difference was observed in the incidence of macrovascular and microvascular complications among the three groups (P>0.05, Table I)

Differences between the low and high glycemic excursion groups. No significant differences were observed in the age, disease course, FPG, HbA1c, SBP, DBP, TC, TG, LDL-C, HDL-C, ALT, AST, BUN, Cre and UA between the low and high glycemic excursions groups (P>0.05). The hs-CRP and BMI levels were significantly higher in the high glycemic excursion group than those in the low glycemic excursion group (P<0.05). No significant difference was observed in the incidence of DM macrovascular and microvascular complications between the two groups (P>0.05, Table II).

Correlation analysis. Pearson's correlation analysis revealed a positive correlation between hs-CRP and MAGE, HbA1c, BMI and macrovascular complications (r=0.71, r=0.43, r=0.55 and r=0.78, respectively; P<0.05).

Multivariate linear regression analysis indicated that there was an independent positive correlation between HbA1c, BMI and hs-CRP (P<0.05, Table III).

Discussion

hs-CRP is a member of the class of acute phase reaction proteins and the hs-CRP level reflects the degree of systemic inflammatory response. A previous study demonstrated that the serum hs-CRP level was high in patients with DM, including those with macrovascular complications. It was also found that high hs-CRP was an independent predictor of cardiac risk in patients with T2DM (19). In the present study 63 patients with poorly controlled T2DM (HbA1c, >7%) were selected, and then divided into three groups according to HbA1c level. The results revealed no significant differences in the age, disease course, BMI, SBP, DBP, FPG, TC, TG, LDL-C, HDL-C, ALT, AST, BUN, Cr, UA, MAGE, SDBG and MODD among the groups and no association was found between HbA1c and glycemic excursion; however, an increase in HbA1c levels triggered an increase in 24 h MBG levels. Meng *et al* (21) observed dynamic glucose characteristics in patients with T2DM with different concentrations of HbA1c through the CGMS for 72 h, and the results showed that the HbA1c levels were positively correlated with the 24 h MBG levels, but not with MAGE, which was consistent with the present results. In addition, the present

Table II. Comparisons between the clinical data of the low and high glycemic excursion groups.

Variables	Low glycemic excursion group (n=26)	High glycemic excursion group (n=37)	P-value
Age (years)	47.58±13.24	55.19±12.61	0.168
Course (years)	8.67 (0.08-15.50)	7.43 (0.01-12.67)	0.702
BMI (kg/m^2)	24.14±1.25	26.33±1.47[b]	<0.001
SBP (mmHg)	132.59±25.20	136.41±26.44	0.754
DBP (mmHg)	81.77±8.93	82.59±8.47	0.869
FPG (mmol/l)	9.62±0.98	10.31±0.87	0.677
HbA1c (%)	9.42±0.76	10.35±0.92	0.451
TC (mg/dl)	168.61±38.05	170.53±42.28	0.842
TG (mg/dl)	251.20±11.96	263.35±14.42	0.658
LDL-C (mg/dl)	89.50±9.29	95.25±9.74	0.53
HDL-C (mg/dl)	48.62±9.79	51.83±10.02	0.492
ALT (U/l)	29.13±7.51	27.91±6.47	0.912
AST (U/l)	21.74±10.29	31.93±10.26	0.507
BUN (mmol/l)	6.59±0.51	5.94±0.65	0.278
Cre (μmol/l)	55.03±11.17	52.16±11.28	0.569
UA (μmol/l)	350.78±90.46	303.81±97.50	0.196
hs-CRP (mg/l)	2.14±0.76	4.05±0.54[a]	0.013
Macrovascular complications, cases (%)	12 (46.15)14 (37.83)		
Microvascular complications, cases (%)	10 (37.00)16 (43.24)		

Values presented are mean ± standard deviation, unless otherwise specified. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, total triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cre, creatinine; UA, uric acid; hs-CRP, high-sensitivity C-reaction protein. [a]P<0.05 and [b]P<0.01 vs. the low glycemic excursion group.

Table III. Multivariate linear regression analysis.

Variables	Regression coefficient	Standard error	t-test	P-value
HbA1c	0.35	0.20	1.92	0.03
BMI	0.18	0.10	1.82	0.04
MAGE	0.09	0.07	1.61	0.06

HbA1c, glycated hemoglobin; BMI, body mass index; MAGE, mean amplitude of glycemic excursion.

study indicated that an increase in HbA1c levels also triggered an increase in hs-CRP levels. Sarinnapakorn *et al* (22) found that hs-CRP levels correlated with HbA1c levels in overweight female patients with T2DM. Kilpatrick *et al* (23) suggested that HbA1c was an independent predictor of the risk of retinopathy and nephropathy in patients with T1DM, and that high HbA1c levels were associated with the risk of cardiovascular mortality in the general Japanese population (24). It was shown in the present study that the increase in HbA1c levels led to an increase in macrovascular complications, which was not statistically significant. This finding was in line with the findings of the aforementioned study (24). In addition, Sartore *et al* (25) indicated that retinopathy was closely associated with the course of DM, but not with HbA1c levels. In the present study, the course of the disease was marginally shorter in groups with low HbA1c levels than in groups with high HbA1c levels; therefore, microvascular complications occurred less often in groups with high HbA1c levels than in those with low HbA1c levels. This suggests that active glucose control, which aims to inhibit the inflammatory response, can be beneficial for the prevention of complications in patients with DM.

MAGE, which is widely used in clinical research, is considered as the gold standard for glycemic fluctuations (26). The Clinical application guide of blood glucose monitoring in China (2011) (20) defines the normal reference standard of glycemic excursion as a MAGE of <3.9 mmol/l. Based on this criterion, the patients enrolled in the study were divided into a low and a high glycemic excursion group. No significant differences were observed in the age, disease course, BMI, SBP, DBP, FPG, HbA1c, TC, TG, LDL-C, HDL-C, ALT, AST, BUN, UA and Cre among the two groups, which suggests that glycemic excursions were not associated with the aforementioned indices. This also demonstrates that HbA1c and MAGE are independent risk factors for glucose control. hs-CRP levels were higher in the high glycemic excursion group than in the low glycemic excursion group, which indicates that the greater the glycemic excursions, the higher the hs-CRP levels. Chang *et al* (27) reported that there was a positive correlation between serum hs-CRP and MAGE in patients with T2DM,

which was in agreement with the results of the present study. Su *et al* (14) reported that MAGE was significantly higher in patients with coronary artery disease than in patients without it. Other studies have reported that glycemic fluctuations are positively correlated with the carotid artery intima-media thickness in patients with T2DM (15,28), suggesting that glycemic excursions are associated with macrovascular complications. The present study confirmed that the incidence of diabetic complications was higher in the high glycemic excursion group than in the low glycemic excursion group, but no significant difference was observed between the two groups. A possible explanation for that could be the limited number of cases included in the study.

Correlation analysis demonstrated that hs-CRP levels were positively correlated with MAGE and HbA1c levels, which indicated that the larger the fluctuation range, the higher the hs-CRP and total glucose levels. Rizzo *et al* (29) found that, following pharmacological intervention, changes in interleukin-6 levels significantly correlated with changes in MAGE in patients with T2DM. Additionally, a reduction in the hs-CRP levels was associated with a reduction in the HbA1c levels (30), which was in line with the present findings. Misra *et al* (18) indicated that hs-CRP levels were higher in patients with T2DM with macrovascular complications than in those with T2DM without macrovascular complications. Another previous study reported the same findings, and also demonstrated that hs-CRP was positively correlated with macrovascular complications (31). The associations between hs-CRP and HbA1c were analyzed using multivariate stepwise regression analysis, and the results indicated that HbA1c was a risk factor for hs-CRP and that glycemic excursions had a smaller effect on the systemic inflammatory response than HbA1c did; therefore, when glycemic control treatment is planned, priority should be given to the reduction of the HbA1c levels followed by the reduction of glycemic excursions. This indicates that reducing the inflammatory response defers the occurrence and development of complications associated with DM.

In conclusion, CGMS is helpful to the doctor in the evaluation of a patient's condition and the subsequent planning of the treatment regimen. Furthermore, HbA1c and MAGE values independently reflect the glucose level. The results of the present study indicate that, when total glucose levels are considerably high, HbA1c levels should be reduced first. The aforementioned practice is very beneficial to the control of the inflammatory response.

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