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Review Article

Serum glycated albumin is superior to hemoglobin A1c for correlating with HMGB1 in coronary artery disease with type 2 diabetic mellitus patients

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Abstract: High mobility group box 1 protein (HMGB1) was significantly increased in coronary artery disease (CAD) with type 2 diabetic mellitus (T2DM) patients. This study was to investigate the relationship between average blood glucose level and HMGB1 level in CAD with T2DM patients. 164 CAD patients were divided into two groups: CAD with T2DM patients group and CAD without T2DM patients group. Glycated albumin (GA) and glycosylated hemoglobin A1c (HbA1c) and HMGB1 concentrations were measured in CAD with T2DM patients. The fasting glucose levels, GA and HbA1c levels were sinificantly increased in CAD with T2DM patients compared to those in CAD without T2DM patients (all $P<0.05$). The hs-CRP levels in CAD with T2DM patients were significantly higher than those in CAD without T2DM patients ($P<0.05$). The HMGB1 levels in CAD with T2DM patients were also significantly higher than those in CAD without T2DM patients ($P<0.05$). Both serum GA levels and HbA1c levels were positively correlated with HMGB1 levels ($n=84$, $r=0.512$ and $r=0.402$, both $P<0.05$). The present study showed that both serum GA levels and HbA1c levels were positively related with HMGB1 levels in CAD with T2DM patients. Increased blood glucose levels may contribute to the increased HMGB1 levels. GA level is superior to HbA1c level for correlating with HMGB1 level.

Keywords: Coronary artery disease, type 2 diabetic mellitus, high mobility group box 1 protein, glycated albumin, glycosylated hemoglobin A1c

Introduction

Inflammation plays a critical role in the initiation, progression and the final steps of atherosclerotic coronary artery disease (CAD) [1]. High mobility group box 1 protein (HMGB1) is a non-chromosomal nuclear protein which could regulate gene transcription and maintain the nucleosome structure, and could be negatively released by necrotic cell or apoptotic cell, or by positively activated innate immune cells (such as macrophages and monocytes) [2, 3]. At present, HMGB1 has been reported to function as a new pro-inflammatory cytokine in cardiovascular diseases [4-6]. Recently, Hu et al [4] showed that serum HMGB1 levels were correlated with the severity of coronary artery stenosis in CAD patients and HMGB1 was an independent factor for CAD. Moreover, elevated HMGB1 levels could also predict adverse clinical outcomes such as heart failure, in-hospital death in patients with ST-segment elevation myocardial infarction after revascularization therapy, myocardial rupture [7, 8]. These results suggest that the change of serum HMGB1 levels may be an independent predictor for cardiovascular diseases.

Diabetes mellitus (DM) patients have been shown to develop an aggressive form of atherosclerosis and could affect their long-term survival for CAD patients. Hyperglycemia is as a critical promoter during the development of cardiovascular diseases. It has been shown that hyperglycemia could promote the genesis of oxidative stress and inflammatory injury which were directly responsible for the progression of atherosclerosis, coronary insufficiency, myocardial infarction and myocytes damage [9]. Yan et al [10] showed that serum HMGB1 levels in CAD

Table 1. Characteristics of CAD with presence or absence of T2DM patients

	Without T2DM (N=82)	With T2DM (N=86)
Age (year)	56.8±9.1	57.2±10.5
Female (%)	35 (41.7)	36 (42.8)
Smoking (%)	24 (30.0)	28 (33.3)
Drinking (%)	21 (26.3)	25 (29.8)
Hypertension (%)	34 (42.5)	34 (40.5)
Aspirin (%)	40 (48.8)	45 (52.3)
β-blocker (%)	30 (36.6)	33 (38.4)
Calcium blocker (%)	26 (32.5)	28 (33.3)
ACEI/ARB (%)	19 (23.8)	23 (27.4)
Statin (%)	15 (18.8)	15 (17.9)
BMI (kg/m^2)	23.9±3.8	24.7±4.2
TC (mmol/L)	4.87±1.07	5.19±1.11
TG (mmol/L)	1.59±0.57	1.69±0.61
HDL-C (mmol/L)	1.16±0.33	0.98±0.38
LDL-C (mmol/L)	3.38±0.87	3.41±0.92
Fasting glucose (mmol/L)	4.83±1.07	7.98±1.15#
GA (%)	10.18±3.65	19.35±4.04#
HbA1c (%)	5.08±0.78	8.94±1.04#
hs-CRP (mg/L)	3.18±0.98	5.82±1.15#
HMGB1 (ng/ml)	5.09±0.91	8.91±1.36#

Data were presented as mean ± SD. CAD, coronary artery disease; T2DM, type 2 diabetes mellitus; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein-cholesterol; GA, glycated albumin; HbA1c, glycosylated hemoglobin A1c; hs-CRP, high-sensitivity C-reactive protein; HMGB1, high mobility group box 1 protein. #P<0.05, compared to without T2DM.

with type 2 diabetes mellitus (T2DM) patients were significantly increased compared to those CAD without T2DM patients. In addition, recent study showed that hyperglycemia could promote the expression of HMGB1 [11]. These results indicates that blood glucose levels may influence serum HMGB1 levels in CAD with T2DM patients. In present study, we investigated the relationship between HMGB1 and average blood glucose level in CAD patients with T2DM.

Materials and methods

Study population and data collection

All clinical protocols in this study conformed with the ethical guidelines outlined in the declaration of Helsinki and were approved by the Institutional Medical Ethics Committee of Huangshi Center Hospital. 164 consecutive patients (age from 30 years old to 75 years old) with CAD who agreed to participate in this study were enrolled between 1 Jan 2012 and 30 Dec 2013. All patients were divided into 2 groups based on presence or absence of T2DM (two fasting plasma glucose levels ≥7.0 mmol/L or two 2 h postprandial plasma glucose readings ≥11.1 mmol/L after a glucose load of 75 g or two casual glucose readings ≥11.1 mmol/L, or parenteral insulin or taking oral hypoglycemic drugs). All patients were performed to selected coronary artery angiography. The patients with the severity of coronary artery luminal diameter narrowing of ≥50% were defined as CAD group. Physical examination, laboratory values, chest roentgenogram, echocardiography with wall motion analysis and Doppler screening were performed to exclude structural heart diseases. Type 1 diabetes mellitus were also excluded by C-peptide measurement. Electrocardiogram and Holter study were performed to exclude arrhythmias in all patients. The exclusion criterias for all subjects were as follows: less than 20 years old, more than 75 years old, variant pectoris, myocardial infarction, chronic coronary artery total occlusion, cardiac dysfunction or having other diseases including fever, arrhythmias, peripheral vascular disease, renal or liver dysfunction, autoimmune disease and cancer.

Sample collection and biochemical investigation

Venous blood (2 ml) was collected from all participants between 06:00 and 07:00 after an overnight fast. Serum samples were centrifuged by 3000 rmp/min at 4°C and then were aliquoted and stored at -70°C until use (approximately 2 month later). Serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low density lipoproteincholesterol (LDL-C), fasting glucose, glycated albumin (GA), glycosylated hemoglobin A1c (HbA1c) and high-sensitivity CRP (hs-CRP) were measured with standard laboratory techniques on a Hitachi 912 Analyzer (Roche Diagnostics, Germany). Serum HMGB1 levels were measured by a commercially available ELISA kit (HMGB1 ELISA kit II; Shino-Test Corporation, Tokyo, Japan) according to its protocol. Drinking, ≥50 g/d white wine within three

Table 2. Pearson corrections of HMGB1 level with cardiovascular risk factors CAD with T2DM patients

Variable	r	p
Age	0.178	NS
BMI	0.156	<0.05
TC	0.124	<0.05
TG	0.113	NS
HDL	-0.156	NS
LDL	0.299	<0.05
GA	0.505	<0.05
HbA1c	0.402	<0.05
hs-CRP	0.417	<0.05

HMGB1, high mobility group box 1 protein; T2DM, type 2 diabetes mellitus; GA, glycated albumin; HbA1c, glycosylated hemoglobin A1c; BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein.

months before this study. Hyperlipidaemia, low-density lipoprotein cholesterol (LDL-C) ≥4.14 mmol/L. Hypertension, systolic pressure ≥140 mmHg or diastolic pressure ≥90 mmHg.

Statistical analysis

Statistical analysis was performed with the SPSS 16.0 (SPSS Inc., Chicago, IL, USA). All values were expressed as mean ± SD or the percentage of incidence. Chi-square test or Fisher's exact test was used to compare proportions. Student *t*-test was used for comparisons between the two groups. Pearson correlation coefficient was used to assess the relationship between serum HMGB1 levels and other cardiovascular risk factors. Statistical significance was accepted at P<0.05.

Results

Clinical characteristics of patients

As shown in **Table 1**, there were no significant differences in mean age, percent of sex, level of lipids (TC, TG, HDL-C and LDL-C), body mass index (BMI), and medication between the two groups (all P>0.05).

However, fasting glucose levels, GA levels and HbA1c levels were significantly increased in CAD with T2DM patients compared to those in CAD without T2DM patients (both P<0.05). There were significant differences in hs-CRP levels and HMGB1 levels (both P<0.05). The hs-CRP levels in CAD with T2DM patients were significantly higher than those in CAD without T2DM patients (P<0.05). The HMGB1 levels in CAD with T2DM patients were also significantly higher than those in CAD without T2DM patients (P<0.05).

Association of HMGB1 levels with cardiovascular risk factors

Corrections of HMGB1 level and some risk factors for cardiovascular disease were shown in **Table 2**. There was a significantly positive correlation between HMGB1 levels and GA levels in CAD with T2DM patients (n=84, r=0.512, P<0.05). The HbA1c levels were also correlated with the HMGB1 levels (n=84, r=0.402, P<0.05). The HMGB1 levels were also correlated with BMI, TC, LDL-C and hs-CRP level in CAD patients with T2DM. There were no significantly positive correlations between HMGB1 and GA or HbA1c levels in CAD without T2DM patients (n=80, r=0.209, P>0.05 or r=0.198, P>0.05).

Discussion

In 2004, Kalinina et al [12] firstly found that HMGB1 was abundantly expressed in atherosclerotic plaques derived from human autopsy specimens. Recently, Hu et al [4] indicated that serum HMGB1 levels were significantly increased in stable angina pectoris and unstable angina pectoris patients, and serum HMGB1 levels were correlated with the severity of coronary artery stenosis in the angina pectoris patients, especially in stable angina pectoris patients, which suggested that increased serum HMGB1 levels may be a new predictor of adverse clinical outcomes of atherosclerotic CAD and may be involved in the development of atherosclerotic CAD. In the present study, we found that serum HMGB1 levels were significantly increased in CAD with and without T2DM patients. Meanwhile, the HMGB1 levels in CAD with T2DM patients were significantly higher than those in CAD without T2DM patients. These were consistent with previous observation [10]. Yan et al [10] showed that the expressions of HMGB1 were closely correlated with the expressions of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and hs-CRP levels in CAD patients. In the present study, we found that the HMGB1 levels were also correlated with the hs-CRP levels in CAD with T2DM

patients. There were cross-talks between HMGB1 and other pro-inflammatory cytokines, such as TNF-α, IL-6 and hs-CRP [3, 13]. Once released from necrotic cell, or apoptotic cell or macrophages, HMGB1 could function as a pro-inflammatory stimulus that up-regulates TNF-α, IL-6, hs-CRP and macrophage inflammatory proteins (MIP-1α and MIP-1β) [3, 13], these indicated that this mechanism reinforced the inflammatory process which contributed to the progression of atherosclerotic CAD [1]. These suggest that HMGB1 may play a critical role in the development of atherosclerotic CAD.

In the present study, we found that both serum GA levels and HbA1c levels were positively related with HMGB1 levels in CAD with T2DM patients. Recently, Zhao et al [14] showed that serum HMGB1 levels was positively related with HbA1c levels in CAD with T2DM patients. Meanwhile, we also found that serum GA levels were superior to HbA1c levels for correlating with HMGB1 levels. Previous study indicated that hyperglycemia has been shown to promote the expression of HMGB1 [11]. In addition, previous studies showed that both GA level and HbA1c level could represent the average blood glucose level and could use to estimate the degree of CAD and the risk of major adverse cardiac events in CAD with T2DM patients [15, 16]. Shen et al [16] further indicated that GA is superior to HbA1c for evaluating the presence and severity of CAD in T2DM patients while HMGB1 levels were correlated with the severity of coronary artery stenosis [4], these indicated that the HMGB1 levels may be more associated with the GA levels in CAD without T2DM patients. Thus, these results suggest that increased blood glucose level may contribute to the increased HMGB1 level and GA is better representative for the recently average blood glucose level and was superior to HbA1c. However, we found that there was no significantly correlation between HMGB1 and GA level in CAD patients without T2DM. This may be attribute to the stable and relatively lower blood glucose level may not stimulate the release of HMGB1. Thus, these need to require future elucidation. In addition, we also found that the HMGB1 levels were also correlated with the LDL-C levels. Recently, Haraba et al [17] indicated that the serum HMGB1 levels were significantly increased and fluvastatin could reduce the serum HMGB1 level. Haraba et al [18] further showed that hyperlipidemia could stimulate the extracellular release of the nuclear HMGB1 while reducing hyperlipidemia may decrease the expression of HMGB1. These results indicated that serum lipid levels may also affect serum HMGB1 levels. These results suggest that controlling blood glucose and lipid level could decrease the HMGB1 level, and then inhibit and delay the progression of atherosclerosis.

Overall, our study included only a small group of Chinese patients, and a future study with a large cohort will be needed. The precise mechanisms underlying our observations require future elucidation.

Conclusion

The present study showed that both serum GA and HbA1c levels were positively related with HMGB1 level in CAD with T2DM patients. Increased blood glucose levels may contribute to the increased HMGB1 levels. While serum GA level is better representative for the recently average blood glucose and GA level is superior to HbA1c level for correlating with HMGB1 level.

Disclosure of conflict of interest

None.

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