

Association of statin use and stress-induced hyperglycemia in patients with acute ST-elevation myocardial infarction

Chen Yan¹, Ma Qin², Yang S Juan¹, Li Y Tao², Gao M dong¹, Zeng Zechun², Yang X Chun³, Cong H Liang¹, Liu Yin¹ and Meng Kang²

Abstract

Background: Only a few information is available on the risk of stress hyperglycemia following acute myocardial infarction after statin use. We investigate the association of stress-induced hyperglycemia following statin use in patients with acute myocardial infarction.

Methods: An observational analysis of 476 consecutive patients who suffered acute myocardial infarction was carried out. All selected patients were divided into diabetes mellitus and non-diabetes based on the presence or absence of diabetes. The cardiac incidence of in-hospital and stress-induced hyperglycemia was recorded.

Results: Among patients with stress hyperglycemia in non-diabetes mellitus subgroups, the average fasting plasma glucose values in statin users were higher than in non-statin users ($P < 0.05$). But in diabetes mellitus subgroups, the average fasting plasma glucose did not have a significant difference between statin users and non-statin users ($P > 0.05$). In non-diabetes mellitus patients, the incidence of stress hyperglycemia with statin therapy was significantly higher than with non-statin therapy ($P = 0.003$). But in diabetes mellitus patients group, there is no significant difference in incidence of stress hyperglycemia between patients with statin therapy and patients without statin therapy ($P = 0.902$). The incidence of heart failure and in-hospital mortality of acute myocardial infarction in patients with stress-induced hyperglycemia was significantly higher than in non-hyperglycemia patients ($P < 0.05$).

Conclusion: Statins are related to higher stress hyperglycemia and cardiac incidences after acute myocardial infarction.

Keywords

Statins, acute myocardial infarction, stress-induced hyperglycemia

Date received: 8 October 2015; revised: 23 November 2015; 25 January 2016; accepted: 27 January 2016

Background

Acute myocardial infarction (AMI), defined as acute coronary occlusion, could result in myocardial ischemia and necrosis. In the early stage of AMI, regardless of diabetes status, stress-induced hyperglycemia increases malignant arrhythmia, cardiac dysfunction, infarct size expansion and poor prognosis.¹ Statins are widely prescribed to lower cholesterol and reduce cardiovascular morbidity and mortality. However, recent studies have reported that long-term use of statins could take effect on glucose metabolism and cause worsening of hyperglycemia and increase the risk of new-onset diabetes.² But several clinical trials released the messages of the balance of cardiovascular benefits and hyperglycemia risk of statin use.^{3–5} At present, the association

between stress hyperglycemia and statin use is not clear. We conducted a retrospective observation of the association between stress-induced hyperglycemia and the use of statins in patients who were hospitalized with AMI in our hospital.

¹Department of Cardiology, Tianjin Chest Hospital, Tianjin, China

²Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

³Department of Cardiology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

Corresponding author:

Meng Kang, Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China.

Email: mengkang1970@hotmail.com



Methods

Patient selection

The subjects were patients admitted with AMI in Beijing Anzhen hospital from January 2010 to December 2010. The study protocol was approved by the Beijing Anzhen hospital ethics committee and informed consent of all patients was obtained. Inclusion criteria are as follows: (1) AMI diagnosis met ST-segment elevation myocardial infarction (STEMI) criteria.⁶ The creatine phosphokinase-MB isoenzyme and/or troponin-T concentration was elevated above the hospital laboratory's myocardial infarction threshold with at least one of the following: ischemic symptoms, persistent ST-T segment changes. (2) The criteria used to label patients diabetic were documentation of the diagnosis in the medical record and those who were prescribed medication for diabetes.⁷ Non-diabetes is defined the patients participated in physical examinations each year and fasting blood glucose was normal (<6.1 mmol/L) with ordinary values of glycosylated hemoglobin (HbA1c). (3) An in-hospital FPG level ≥ 8 mmol/l was considered stress hyperglycemia.⁸ (4) The patients were over 18 years of age. (5) Patients who were prescribed chronic statin therapy were defined as patients who received a moderate-dose statin therapy at least six months (including: Rosuvastatin 10 mg, Simvastatin 20–40 mg, Pravastatin 20–40 mg, Atorvastatin 20 mg, fluvastatin 80 mg). (6) Non-statin use is defined as patients in cohort with no prescription for statins prior to admission.

Exclusion criteria

(1) Patients who had been diagnosed with hyperthyroid and were receiving treatment; (2) Patients with Cushing's syndrome or other diseases that affected glucose metabolism; (3) in the face of other stressors, such as severe infection, sepsis, surgery or trauma, et al. (4) Hepatic insufficiency; (5) Renal insufficiency. All patients diagnosed with AMI received detailed inquiry about their medical history, comorbidities and concomitant medications. The fasting blood glucose (FBG) was examined at 6 a.m. every morning from the first to the seventh day after admission. Blood glucose was measured using glucose meters (Roche). All patients with AMI received percutaneous transluminal coronary angioplasty or thrombolytic therapy according to ACC/AHA treatment guidelines based on their treatment time and risk stratification. All the patients were divided into diabetes mellitus (DM) and non-diabetes mellitus group based on the presence or absence of DM, and we investigated the association of statin use and stress-induced hyperglycemia.

Statistics

SPSS 17.0 (SPSS, Inc., Chicago, IL, USA) software was applied by a professional statistics to complete the analyses. Continuous variables were expressed as mean with standard deviation. Comparisons between continuous variables were performed using the t test or analysis of variance. Categorical variables were expressed as frequency and percentage. Comparisons between categorical variables were compared using the Chi-square test or Fisher's exact test. A P-value of ≤ 0.05 was considered statistically significant.

Results

Four hundred and seventy-six patients who met the inclusion criteria were enrolled in this clinical observation. The frequency of in-hospital stress hyperglycemia was 20.17% (96/476) and that of statin use was 31.72% (151/476). The most prevalent prescribed statin was Atorvastatin (37.74% (57/151)), followed by Simvastatin (23.18% (35/151)), Rosuvastatin (18.54% (28/151)), Fluvastatin (11.26% (17/151)) and Pravastatin (9.27% (14/151)). Different categories of statin have similar effects on stress hyperglycemia in patients with or without diabetes.

Stress hyperglycemia was analyzed in DM and non-DM subgroups.

In non-DM patients group, 15.10% (37/245) stress hyperglycemia were documented in 245 patients of non-statin therapy, whereas a total of 29.89% (26/87) stress hyperglycemia developed in the 87 statin therapy patients. The incidence of stress hyperglycemia in the statin therapy was significantly higher than in the non-statin therapy ($P = 0.003$).

In DM patients group, the incidence of stress hyperglycemia in patients without taking statins was 28.75% (23/80), while the incidence of stress hyperglycemia in patients with taking statins was 29.69% (19/64). There is no statistical significant difference in incidence of stress hyperglycemia between patients on statin therapy and patients without statin therapy ($P = 0.902$).

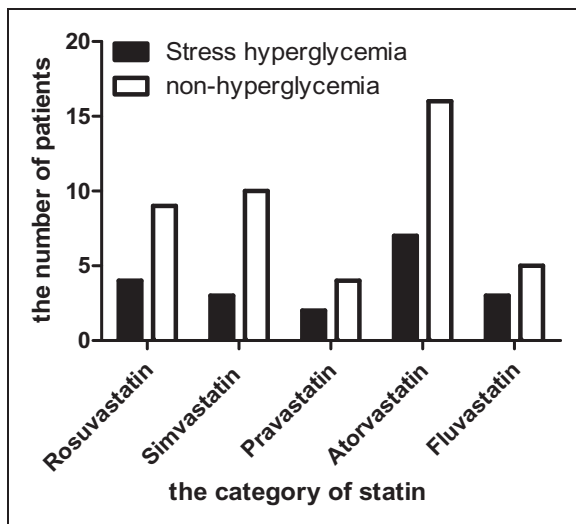
Among patients with stress hyperglycemia in non-DM subgroups, the average FPG values were 8.24 ± 2.61 mmol/l in statin users, compared with 7.58 ± 2.32 mmol/l in non-statin users, and there was a significant difference between the two groups ($P = 0.028$). However, among patients with stress hyperglycemia in DM subgroups, the average FPG values were 9.71 ± 3.08 mmol/l in statin users, compared with 10.23 ± 3.24 mmol/l in non-statin users, and there was no significant difference between the two groups ($P > 0.05$).

Table 1 shows the basic characteristics of the selected patients both DM and non-DM. Figure 1 shows the incidence of stress hyperglycemia in different categories of statins in DM patients. There was no significant difference between the groups ($P > 0.05$). Figure 2 shows

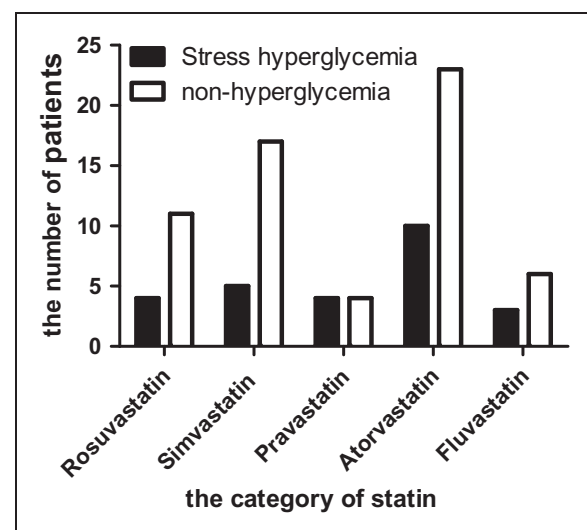
Table 1. Baseline characteristics of patients with and without DM.

Glycemic status	Patients number (n)	Male (n (%))	Age (years)	BMI (kg/m ²)	EF (%)
Patients with DM	144	98 (68.06%)	58.60 ± 12.34	25.15 ± 2.23	53.32 ± 6.89
Patients without DM	332	237 (71.39%)	59.24 ± 12.41	24.74 ± 3.11	55.26 ± 7.73
	WBC (×10 ⁹ /L)	HGB (g/l)	PLT (×10 ⁹ /L)	LDL-C (mmol/l)	HDL-C (mmol/l)
Patients with DM	7.45 ± 2.00	133.70 ± 18.62	219.92 ± 64.62	2.78 ± 0.74	1.12 ± 0.33
Patients without DM	7.39 ± 4.79	130.12 ± 20.19	213.62 ± 55.61	2.82 ± 0.77	1.15 ± 0.30
	CRP	TG (mol/l)	CRE (μmol/l)	ALT(μ/l)	History of hypertension (n (%))
Patients with DM	8.94 ± 6.07	2.07 ± 1.64	61.38 ± 20.47	20.43 ± 18.86	79 (54.86%)
Patients without DM	9.67 ± 8.77	1.87 ± 0.65	62.81 ± 20.54	21.63 ± 11.73	175 (52.71%)
	History of coronary heart disease (n (%))	Smoking (n (%))	Drinking	Statin (n (%))	Glucose level
Patients with DM	83 (57.64%)	61 (42.36%)	63 (43.75%)	64 (44.44%)	8.69 ± 3.17
Patients without DM	178 (53.61%)	155 (46.69%)	161 (48.49%)	87 (26.20%)	7.75 ± 2.41

BMI: body mass index; WBC: white blood cells; HGB: hemoglobin; PLT: platelets; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; CRE: creatinine; ALT: alanine transaminase; EF: ejection fraction;

**Figure 1.** Correlation between different category of statin and the number of hyperglycemia in patients with DM.

the incidence of stress hyperglycemia in different categories of statins in non-DM patients. There was no significant difference between the groups ($P > 0.05$). Figure 3 shows the correlation between time of AMI and FBG in the non-diabetic group. FBG values

**Figure 2.** Correlation between different categories of statin and the number of hyperglycemia in patients without DM.

reached a maximum two days after AMI and then decreased gradually; the blood glucose values were significantly different at two days after AMI between statin use and non-statin use ($P < 0.05$). From the first to the seventh day after admission, the number of high

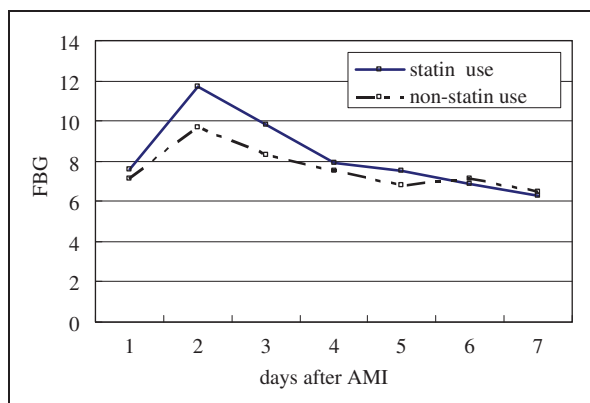


Figure 3. Correlation between time of AMI and FBG in the non-diabetic group.

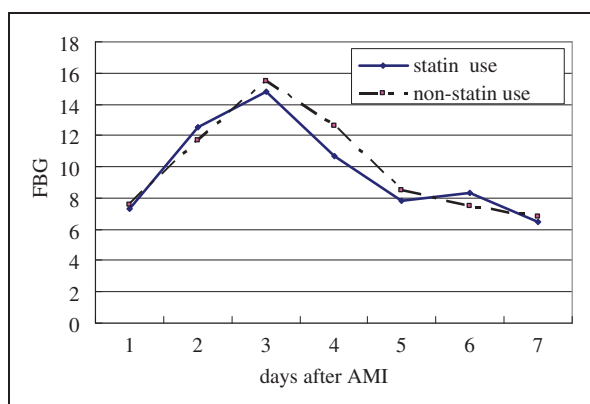


Figure 4. The correlation between time of AMI and FBG in the DM group.

blood glucose levels which were required to label stress hyperglycemia was two. Figure 4 shows the correlation between time of AMI and FBG in the DM group. FBG values reached a maximum three days after AMI and then decreased gradually. There was no difference between statin use and non-statin use ($P > 0.05$). From the first to the seventh day after admission, the number of high blood glucose levels which were required to label stress hyperglycemia was four. Table 2 shows characteristics of myocardial infarction in statin user with and without stress-induced hyperglycemia. The incidence of heart failure, in-hospital mortality of AMI in patients with stress-induced hyperglycemia was significantly higher than in the non-hyperglycemia patients (22.22% vs. 8.49%, 13.33% vs. 3.77%, $P < 0.05$).

Discussion

During stress response, activation of serial hormones like glucocorticoid, glucagon, adrenaline, thyroxin and others induces insulin resistance resulting in

hyperglycemia. It is well known that stress hyperglycemia is associated with oxidative stress, inflammatory responses, damaging of coronary microcirculation and markedly worsened signal transduction pathways of endogenous cardio-protective responses. Hyperglycemia can induce ADP-induced platelet aggregation and increase plasma catecholamine, which is associated with vulnerable plaque evolution, promotion of microcirculatory dysfunctions and thrombogenesis.^{9–18} Acute hyperglycemia is a common feature in patients with AMI associated with a direct detrimental effect on ischemic myocardium, and it is one of the main reasons for the increased short- and long-term mortality risks.¹⁹

Statins are one of the drugs widely used in clinical practice. For patients with coronary heart disease or risk factors for coronary heart disease, statins can reduce the incidence of cardiovascular events. Statins have been confirmed to be relatively well tolerated and they are effective drugs in significantly lowering LDL-C; they increasingly encourage the reduction of cardiovascular morbidities and mortalities.^{2,20} However, meta-analysis has recently shown that statins can moderately or significantly increase the risk of new-onset diabetes.²⁰

Despite multiple clinical trials and meta-analyses^{21–23} suggesting a link between statin use and the risk of T2D, few studies have been conducted to investigate the association between statin use and stress hyperglycemia in patients with AMI. It is necessary to identify the possible effect of statin therapy in the development of stress-induced hyperglycemia.

Our study indicated that the overall incidence of stress hyperglycemia was 20.17% (96/476) in patients after AMIs. The incidence of stress hyperglycemia in the statin therapy was significantly higher than in the non-statin therapy in patients without DM (29.89% vs. 15.10%, $P = 0.003$). But in the DM patients, statin therapy did not have comparable incidence of stress hyperglycemia than in patients without statins (28.75% vs. 29.69%, $P = 0.902$). The average FPG values in statin users were higher than in non-statin users ($P = 0.028$) among patients with stress hyperglycemia in subgroups without DM. But in DM subgroups, the average FPG values did not have a significant difference between statin users and non-statin users ($P = 0.796$). The FBG values reached a maximum two days after AMI in the non-diabetic group and were significantly higher in non-diabetic patients with statin use at two days after AMI. In DM group, FBG values reached a maximum three days after AMI, but there was no significant difference between statin use and non-statin use. This indicates that statin use was associated with stress hyperglycemia in patients without DM after AMI, but not in DM. Our study showed that statin use did not increase the risk of stress hyperglycemia in DM patients, but the risk of stress hyperglycemia was higher in patients without DM.

Table 2. Characteristics of myocardial infarction in patients prescribed chronic statin therapy with and without stress-induced hyperglycemia.

Variables	Patients with stress-induced hyperglycemia (n = 45)	Patients without stress-induced hyperglycemia (n = 106)	P
Maximum CPK-MB (μ l)	323.20 \pm 105.93	274.07 \pm 125.53	0.023
Infarct location (n (%))			0.960
Anterior/lateral/antroseptal	21 (46.67)	49 (46.23)	
Inferior/posterior/right ventricular	24 (53.33)	57 (53.77)	
Cardiac death (n (%))	6 (13.33)	4 (3.77)	0.031
Complication after AMI (n (%))			
Cardiogenic shock	4 (8.87)	7 (6.60)	0.621
Heart failure	10 (22.22)	9 (8.49)	0.020
Cardiac rupture (n (%))	1 (2.22)	2 (1.89)	0.893
Cardiac arrhythmia	37 (82.22)	85 (80.19)	0.772

AMI: acute myocardial infarction; STEMI: ST-segment elevation acute myocardial infarction; NSTEMI: CPK-MB: creatine phosphokinase-MB; Cardiac arrhythmia: ventricular arrhythmia (ventricular tachycardia /ventricular fibrillation), atrial arrhythmia (atrial tachycardia/atrial fibrillation), bradyarrhythmia (sinus bradyarrhythmia/atrioventricular block).

Recent studies demonstrated that statins was related to cause hyperglycemia and increase the risk of new-onset type 2 diabetes (T2D).²⁴⁻²⁷ Statin therapy has been reported to irreversibly affect mitochondrial function, especially skeletal muscle cells,²⁸ which is the basis of hyperglycemia. Statins modulate insulin secretion and appear to have effect on sensitivity. Some trials data have revealed that statins cause β -cell insulin secretory dysfunction and lead to insulin resistance.

In our study, we failed to find any difference effect on stress hyperglycemia in all types of statins. It appeared that different categories of statins had similar effects on stress hyperglycemia both in DM and non-DM patients. We confirmed that statins' category did not contribute to the incidence of stress hyperglycemia. Our present work indicates that for non-DM patients, chronic statin use play a key role in the risk of developing stress-induced hyperglycemia.

Conclusions

Statins have an effect on the increased the risk of stress-induced hyperglycemia in non-diabetic patients after AMI. Clinicians should monitor fasting glucose level for at least one week to manage non-diabetes patients on statins after AMI.

Limitations

A limitation of our study is that we did not investigate the effect of inflammatory factors and/or stress hormones on FBG levels. Moreover, in non-DM subgroups, patients were not accurately diagnosed for DM in the longer term, and we did not know

controlling glucose levels in these patients is necessary. We do not know if the same patients would exhibit an enhanced stress hyperglycemia in the face of other stressors, such as sepsis, surgery or trauma. But this study addresses the importance and avails evidence for the correlation between statin use and stress-induced hyperglycemia from a clinical perspective. This is a retrospective cohort, it is possible that this type of observational study can conclude a statistical association but causal association cannot be proved.

Ethical approval

Informed consent was obtained from each patient on the day of admission. The study protocol conforms to the ethical guidelines of the World Medical Association. The Hospital Beijing Anzhen Ethics Committee approved the protocol, and all patients gave their informed consent for the inclusion in the study.

Guarantor

Mengkang is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgements

The authors profusely thank Professor Zeng Zechun for giving key advices in the study design and data statistics. The authors also thank the patients who participated in this study.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Contributorship

Chen Yan, Ma Qin contributed equally in this article. Chen Yan, Ma Qin, designed the study and wrote the first draft of the manuscript. Gao Ming Dong, Yang Shou Juan and Li Yun Tao collected the data. Meng Kang and Zeng Zechun reviewed and analyzed the data, researched data, analyzed samples and edited the manuscript. Yang Xin Cun, Liu Yin, Cong Hong Liang conducted the study and managed the data collection.

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