Stress-Induced Hyperglycemia After Hip Fracture and the Increased Risk of Acute Myocardial Infarction in Nondiabetic Patients

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OBJECTIVE—To investigate the risk of acute myocardial infarction (AMI) following stress hyperglycemia after hip fracture.

RESEARCH DESIGN AND METHODS—From February 2007 to February 2012, we carried out a prospective observational analysis of 1,257 consecutive patients with no history of diabetes who suffered hip fractures. Fasting blood glucose (FBG) and glycosylated hemoglobin tests as well as electrocardiography, ultrasonic cardiography, and chest X-ray examinations were performed after admission. All selected hip fracture patients were divided into stress hyperglycemia and non-hyperglycemia groups according to their FBG, and the incidence of AMI was monitored.

RESULTS—Among the patients enrolled, the frequency of stress hyperglycemia was 47.89% (602/1,257) and that of AMI was 9.31% (117/1,257), and the occurrence of AMI in the stress hyperglycemia group was higher than in the non-hyperglycemia group (12.46 vs. 6.41%, P < 0.05). In all patients with AMI, non-ST-segment elevation myocardial infarction occurred more often than ST-segment elevation myocardial infarction (62.39% [73/117] vs. 37.61% [44/117]).

CONCLUSIONS—Stress-induced hyperglycemia after hip fracture increased the risk of AMI.

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With prolonged life span, there is an increasing number of elderly people with aging-related degenerative diseases. Hip fracture is a main complication of osteoporosis among aged patients (1), and prevention of hip fracture-related complications has become increasingly important, mainly focusing on diagnosis and therapy of pulmonary embolism and bronchopneumonia. On the other hand, the risk of acute myocardial infarction (AMI) after hip fractures is not well recognized and has not been given its deserved attention (2), because adverse cardiovascular events were one of the main reasons for an increased mortality risk after hip fracture (3). Besides, research has confirmed an association between risk of cardiovascular events and osteoporosis in older men (4). Hip fractures lead to injuries of the musculoskeletal system and induce a stress state simultaneously, thereby stimulating the release of stress hormones and reducing insulin sensitivity through neuroendocrine changes. As a result, a derangement of glucose metabolism and occurrence of stress hyperglycemia is triggered (5,6), but at present, the epidemiology of stress hyperglycemia is not clear (7). There are conflicting opinions about the disadvantages and influence as well as treatments of stress hyperglycemia, and only a little information is available about the risk of AMI following stress hyperglycemia after hip fractures (8,9). We conducted a prospective clinical observation of the relationship between stress-induced hyperglycemia and AMI in nondiabetic patients who were hospitalized with acute hip fractures in our hospital.

RESEARCH DESIGN AND METHODS

Patient selection
We performed a prospective observational study at the Tianjin Hospital. Consecutive hip fracture patients (n = 1,257) were selected for the analysis during a 5-year period from February 2007 to February 2012. The study protocol was approved by the Tianjin Hospital ethics committee, and informed consent of all patients was obtained. The inclusion criteria were 1) the injury time of hip fractures was <24 h before admission and fracture diagnosis by X-ray examinations in our emergency department, 2) patient participated in physical examinations each year and blood glucose was normal (<6.1 mmol/L) with ordinary values of glycosylated hemoglobin (HbA1c), 3) a pair of lower limb venous vascular ultrasound examinations confirmed no deep venous thromboembolism (DVT), 4) osteoporosis was confirmed by bone density examination, and 5) orthopedic surgery was not completed within 1 week after admission to the hospital or no operation was performed (conservative treatment). The exclusion criteria were 1) the time of hip fracture injury was >24 h before admission; 2) diagnosed type 1 or type 2 diabetes; 3) need of emergency operation; and 4) any signs of deep venous thromboembolism (DVT).
within 1 week after hip fracture; 4) the occurrence of DVT, pulmonary embolism, or thyroid disease; and 5) renal/liver failure.

Procedures
Blood and urine routine, liver and kidney function, calcium, phosphorus, and serum cardiac enzyme concentrations, insulin level, and serum lipids were tested after admission. Electrocardiography (ECG), cardiorespiratory function test, ultrasonic cardiography, chest X-ray, lower limb venous vascular ultrasound, and bone mineral density measurements of the bilateral hip were conducted. Closed reduction, bone traction treatments, and prevention of DVT were administered to all patients with hip fractures on the day of admission (10) and they continued to take their cardiac medications. All patients who met the inclusion criteria were recorded with a standardized form throughout the study course. The fasting blood glucose (FBG) was examined at 6:00 A.M. every morning from the 1st to the 7th day after admission, and ECGs were measured at admission and from the 1st to the 7th day after admission at 10:00 A.M. every morning. If clinical symptoms indicated and/or electrocardiographic changes suggested a myocardial infarction, additional blood samples were drawn from the antecubital vein in order to examine creatine kinase (CK), CK-MB isoenzyme, and troponin-I values. AMI diagnosis met ST-segment elevation myocardial infarction (STEMI) or non–ST-segment elevation myocardial infarction (NSTEMI) criteria (11,12). AMI diagnosis criteria met at least two of following: 1) the CK-MB isoenzyme and/or troponin-I concentration elevated above the hospital laboratory’s myocardial infarction threshold; 2) persistent ST-T segment changes, new Q waves, or left bundle branch block occurred; 3) serious precordial chest pain lasting for 30 min or more. Stress hyperglycemia diagnosis criteria were as follows: 1) patients did not have a previous diabetes history, 2) admission or in-hospital fasting plasma glucose levels of 7 mmol/L or more in two or more tests (13), and 3) normal HbA1c values.

Statistical analyses
SPSS 17.0 (SPSS, Inc., Chicago, IL) software was applied by a professional statistician to complete the analyses. Continuous variables were expressed as mean with SD. Comparisons between continuous variables were performed using the Student t test or ANOVA. Categorical variables were expressed as frequency and percentage. Comparisons between categorical variables were compared using the $\chi^2$ test or Fisher exact test. Multiple logistic regression analysis identified risk factors of AMI. P value $\leq 0.05$ was considered statistically significant.

Clinical follow-up
The period of follow-up interviews was 3 months after discharge, and mortality was

Table 1—Basic characteristics of the selected patients

| Variables               | Stress hyperglycemia (n = 602) | Non-hyperglycemia (n = 655) | $P$  |
|-------------------------|---------------------------------|-----------------------------|------|
| Age (years)             | 75.30 ± 7.78                    | 75.10 ± 7.59                | 0.198|
| Male, n (%)             | 221 (36.71)                     | 225 (34.35)                 | 0.382|
| BMI (kg/m²)             | 23.65 ± 2.96                    | 23.80 ± 2.92                | 0.068|
| HDL-C (mmol/L)          | 1.17 ± 0.22                     | 1.18 ± 0.24                 | 0.393|
| LDL-C (mmol/L)          | 2.56 ± 0.39                     | 2.52 ± 0.33                 | 0.066|
| Triglyceride (mmol/L)   | 1.20 ± 0.31                     | 1.18 ± 0.29                 | 0.099|
| Admission glucose (mmol/L) | 7.51 ± 0.56                | 5.28 ± 0.30                 | 0.000|
| HbA1c (mmol/mol)        | 35.85 ± 3.93                    | 35.62 ± 3.99                | 0.293|
| %                       | 5.43 ± 0.35                     | 5.41 ± 0.36                 | 0.289|
| Insulin level (IU/mL)   | 9.04 ± 2.42                     | 8.88 ± 2.74                 | 0.274|
| CRE (µmol/L)            | 70.58 ± 14.59                   | 69.95 ± 13.71               | 0.430|
| ALT (units/L)           | 24.26 ± 6.23                    | 23.96 ± 6.78                | 0.429|
| EF (%)                  | 57.12 ± 5.63                    | 56.93 ± 5.65                | 0.548|
| Smoking, n (%)          | 185 (30.73)                     | 169 (25.80)                 | 0.052|
| Hypertension, n (%)     | 349 (57.97)                     | 376 (57.40)                 | 0.838|
| CAD/family history of   | 303 (50.33)                     | 325 (49.62)                 | 0.800|
| Drug, n (%)             | Statin                          |                             |      |
|                        | 151 (25.08)                     | 135 (20.61)                 | 0.059|
|                        | ACE-I/ARB                       |                             |      |
|                        | 365 (60.63)                     | 393 (60.00)                 | 0.819|
|                        | β-Blocker                       |                             |      |
|                        | 257 (42.69)                     | 268 (40.92)                 | 0.524|

ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; CRE, serum creatinine; EF, left ventricular ejection fraction.

Figure 1—Correlation between the days after fracture and FBG.
Stress-induced hyperglycemia

recorded by the investigators via telephone calls and/or outpatient clinic visits.

RESULTS—Patients (n = 1,257) who met the inclusion criteria were enrolled in this clinical observation. Among the patients, the average age was 75.20 ± 7.71 years and 64.52% were women. The most prevalent comorbidity was hypertension (57.68%), followed by coronary artery disease (CAD) or family history of CAD (49.90%), dyslipidemia (elevation of LDL cholesterol [LDL-C], 49.27%; triglyceride, 39.14%; and low levels of HDL cholesterol [HDL-C], 21.40%), obesity (37.63%), and smoking (28.16%).

The frequency of stress hyperglycemia was 47.89% (602/1,257) and that of AMI was 9.31% (117/1,257). Table 1 shows the basic characteristics of the selected patients. There was a significant difference in admission glucose levels between the two groups. Figure 1 shows the correlation between time of fracture and FBG. In the stress hyperglycemia group, FBG values reached a maximum 2–3 days after hip fracture and then decreased gradually. Repeated ANOVAs showed that at each time point in the stress hyperglycemia group, the blood glucose values were significantly different (P < 0.05), whereas in the non-hyperglycemia patients, they did not change (P = 0.10) (Fig. 1). Table 2 shows characteristics of myocardial infarctions in the two groups. The incidence of AMI in the stress hyperglycemia group was significantly higher (12.46% [75/602]) than in the non-hyperglycemia group (6.41% [42/655], P < 0.05). The number of AMIs was significantly higher (12.46% [75/602]) than in the non-hyperglycemia patients (6.41% [42/655], P = 0.000).

CONCLUSIONS—In our study, we found that the frequency of stress hyperglycemia was 47.89% and the incidence of AMI was 9.31% in patients after hip fractures. The incidence of AMI in the stress hyperglycemia group was 12.46%, whereas the overall AMI incidence in patients without hip fractures in China is 2.6% (14), indicating that the incidence of AMI in patients after hip fractures appears higher than overall AMI incidence in China.

Others have reported that the increased incidence of AMI after hip fracture was related to osteoporosis (4,14). Osteoporosis and cardiovascular diseases share

Table 2—Characteristics of myocardial infarction in the two groups

| Variables                             | AMI with stress-induced hyperglycemia (n = 75) | AMI without stress-induced hyperglycemia (n = 42) | P  |
|---------------------------------------|-----------------------------------------------|-----------------------------------------------|----|
| Number of AMI, n (%)                  | 75 (64.10)                                    | 42 (35.90)                                    | 0.000 |
| Correlation between days after fracture and AMI occurrence |                                 | 0.021                                        |    |
| ≤3 days, n (%)                        | 47 (60.77)                                    | 28 (66.67)                                    |    |
| >3 days, n (%)                        | 28 (33.33)                                    | 15 (35.71)                                    |    |
| STEMI, n (%)                          | 34 (45.33)                                    | 10 (23.81)                                    | 0.000 |
| NSTEMI, n (%)                         | 41 (54.67)                                    | 32 (76.19)                                    | 0.145 |
| Maximum CPK-MB (units/L)             | 302.12 ± 128.85                               | 268.05 ± 122.03                               | 0.165 |
| Infarct location                      |                                               |                                              |    |
| Anterior/lateral/anteroseptal, n (%)  | 34 (45.33)                                    | 18 (42.86)                                    |    |
| Inferior/posterior/right ventricular, n (%) | 41 (54.67)                                    | 24 (57.14)                                    |    |
| Cardiac death, n (%)                  | 13 (17.33)                                    | 5 (11.90)                                     | 0.435 |
| Complication after AMI                |                                               |                                              |    |
| Cardiogenic shock, n (%)              | 9 (12.00)                                     | 5 (11.90)                                     | 0.988 |
| Heart failure, n (%)                  | 27 (36.00)                                    | 8 (19.05)                                     | 0.055 |
| Ventricular septal perforation, n (%) | 0 (0.00)                                      | 0 (0.00)                                      |    |
| Cardiac arrhythmia, n (%)             | 64 (85.33)                                    | 35 (83.33)                                    | 0.774 |
| Treatments                            |                                               |                                              |    |
| PCI, n (%)                            | 22 (29.33)                                    | 13 (30.95)                                    | 0.845 |
| Thrombolytic and/or anticoagulant therapies, n (%) | 53 (70.67)                                    | 29 (69.05)                                    |    |

Cardiac arrhythmia includes ventricular arrhythmia/atrial arrhythmias/bradyarrhythmia. CPK-MB, creatine phosphokinase-MB; PCI, percutaneous coronary intervention.

Table 3—Risk factors of AMI

| Risk factors          | P     | RR      | 95% CI      |
|-----------------------|-------|---------|-------------|
| Age                   | 0.567 | 0.149   | 0.714–1.851 |
| Male                  | 0.613 | 1.131   | 0.701–1.824 |
| BMI                   | 0.950 | 1.015   | 0.639–1.613 |
| HDL-C                 | 0.615 | 0.872   | 0.512–1.485 |
| LDL-C                 | 0.849 | 0.953   | 0.582–1.562 |
| Triglyceride          | 0.890 | 1.024   | 0.689–1.537 |
| Hypertension          | 0.841 | 0.958   | 0.609–1.056 |
| Smoking               | 0.451 | 0.835   | 0.524–1.333 |
| Stress hyperglycemia  | 0.000 | 2.130   | 1.431–3.172 |
| Statin                | 0.358 | 0.789   | 0.476–1.307 |

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common risk factors like poor general health status, lifestyle, nutrition, hormone secretion, vitamin D deficiency, systemic inflammation-related (e.g., C-reactive protein, interleukin-6, or tumor necrosis factor) diseases, and medications through different mechanisms both in bone and arteries (15–25).

Patients with osteoporotic fractures are likely to have coexisting blood vessel diseases, but in our study, we found that particularly stress hyperglycemia plays a vital role, because the incidence of AMI in the stress hyperglycemia group was 2.130 higher than in the non-hyperglycemia group. In patients with hip fractures, stress hyperglycemia was the sole significant independent risk factor for the development of AMI (95% CI 1.431–3.172).

Acute fractures induce stress hormone secretion of glucocorticoid, glucagon, adrenaline, thyroxin, somatotropin, and others, which is called the “stress response.” During the stress response, activation of serum hormones induces insulin resistance, resulting in hyperglycemia and the associated risk factors present then in patients with acute trauma (26). 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 cardioprotective responses. Hyperglycemia can induce ADP-induced platelet aggregation and increase plasma catecholamine, which is associated with vulnerable plaque evolution, the promotion of microcircular dysfunctions, and thrombogenesis (27–37).

Our present work indicates that for patients without a history of diabetes, stress-induced hyperglycemia plays a key role in the risk of developing AMI. Our present analysis revealed that most (62.67% [47/75]) AMIs occurred within the first 3 days after hip fractures, which is in accordance with the literature (2). In the stress hyperglycemia group, blood glucose peaked at 2–3 days after hip fracture and then declined gradually, indicating a coincidence of AMI with the peak time of FBG. The cause of a more frequent STEMI occurrence in stress-induced hyperglycemia might be that raised glucose levels contribute to platelet activation and thereby enhanced platelet-mediated thrombogenesis (38), which develops into completely occlusive thrombi. In addition, our study showed stress hyperglycemia ranges of 6.1–9.7 mmol/L after hip fractures for the first time, and we recommend that stress-induced hyperglycemias after hip fracture should be identified early.

A limitation of our study was that we did not investigate an effect of inflammatory factors and/or stress hormones on FBG levels, which lead to increased AMI risk. In addition, we did not compare the results of this study with patients suffering from diabetes, and we did not find differences between the stress hyperglycemia and no hyperglycemia groups regarding comorbid disorders and/or drug administrations, e.g., statin against hypertension. Therefore we cannot completely rule out that other factors also contributed to the incidence of myocardial infarctions. Moreover, patients were not accurately diagnosed for diabetes in the longer term, and because blood glucose levels largely fluctuate, we did not specifically treat the hyperglycemias. Up until now, there has been no clear agreement on whether it is necessary to control glucose levels in these patients. In addition, we only show the significance of hyperglycemia on the incidence of AMI during admission; we did not show clinical outcome data at follow-up. However, this study underlines the importance of understanding the indication for adopting appropriate methods to identify stress-induced hyperglycemia in correlation with AMI after hip fracture.

We recommend that in patients, even without previous diabetes, FBGs and ECGs should be monitored for at least the first 7 days after hip fractures. This might be helpful for the endocrinologist, cardiologist, and orthopedic surgeon to timely detect AMIs.

We conclude that stress-induced hyperglycemia increased the risk of AMI in patients with hip fractures. Stress-induced hyperglycemias after hip fracture should be identified early.

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Y.C. designed the study, collected the data, and wrote the first draft of the manuscript. X.Y., K.M., and Z.Z. designed the study and reviewed and analyzed the data. B.M. and X.L. conducted the study. B.Q. researched data and analyzed samples. S.C., P.C., and Y.Y. researched data, analyzed samples, and conceived and edited the manuscript. B.Q. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors thank Dr. Guosheng Xing (Tianjin Hospital, Tianjin, China) who managed the data collection. The authors also thank the people with hip fractures who participated in this study.

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