The Review of DIABETIC STUDIES

ORIGINAL DATA

# The Prognostic Significance of Serum Glucose Levels After the Onset of Ventricular Arrhythmia on In-Hospital Mortality of Patients with Acute Coronary Syndrome

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Manuscript submitted April 20, 2008; resubmitted May 25, 2008; accepted May 29, 2008.

## ■ Abstract

BACKGROUND: Several studies have illustrated the role played by serum glucose levels in cardiovascular morbidity and mortality in general and, more particularly, after an acute coronary event. AIM: The aim of this study was to evaluate the impact of serum potassium and glucose levels on in-hospital mortality in patients with ischemic heart disease, who exhibited severe ventricular arrhythmia. METHODS: We enrolled 162 consecutive patients who were referred to our institution for an acute coronary event and presented with sustained ventricular tachycardia or ventricular fibrillation during the first 24 hours of hospitalization. Serum potassium and glucose levels were measured in all patients at the onset of tachycardia and after 2, 4, 6, 12, 36, 48 hours. RESULTS: During hospitalization, 23 out of 162 patients died (61% males). Serum glucose levels at the onset of the arrhythmia, as well as after 2, 12, 36 and 48 hours, were higher in the deceased (onset: 228.8 ± 108 vs. 158 ± 68 mg/dl, p = 0.0001, 2 h: 182 ± 109 vs. 149 ± 59 mg/dl, p = 0.03, 12 h: 155.5 ± 72 vs. 128 ± 48 mg/dl, p = 0.025, 36 h: 163.8 ± 63 vs.116 ± 42 mg/dl, p = 0.002, and 48 h: 138 ± 64 vs. 122 ± 42 mg/dl, p = 0.05, respectively), even after adjustment for age, sex, diabetes, left ventricular ejection fraction, type of acute coronary syndrome and site of infarction and medication intake. There was no difference in serum potassium levels between the deceased and survivors. CONCLUSION: Serum glucose levels at the onset of arrhythmia and 2, 36 and 48 hours later seem to have prognostic significance for in-hospital mortality in patients hospitalized for an acute coronary event, who exhibit severe ventricular arrhythmia.

**Keywords**: arrhythmia · acute coronary syndrome · myocardial infarction · glucose · hyperglycemia · potassium

## Introduction

Diabetes mellitus is one of the fastest growing public health problems in both developed and developing countries. It has been estimated that the number of people with diabetes in the world will double during the next 25 years [1]. Mortality among individuals with type 2 diabetes is substantially elevated compared with non-diabetics and cardiovascular disease (CVD) accounts for > 75% of total diabetic deaths [2]. These differences can be partly attributed, in patients with ST-segment-elevation myocardial infarction (STEMI), to the larger infarct size and lower left ventricular ejection fraction found in patients with diabetes [3]. In patients with STEMI undergoing thrombolysis or primary PCI, diabetes is independently associated with decreased myocardial reperfusion, larger infarct size, development of congestive heart fail-

ure and decreased survival [4, 5]. Additionally, ventricular tachycardia is a common clinical occurrence during hospitalization for an acute coronary event. It is strongly related to left ventricular remodeling and has an adverse impact on clinical prognosis [6]. The impact of serum potassium and glucose levels on in-hospital mortality in these patients has not been well documented in the literature.

The purpose of this study is to evaluate the role of serum potassium and glucose levels on in-hospital mortality in patients who exhibited sustained ventricular tachycardia or ventricular fibrillation during hospitalization for an acute coronary event.

## Methods

*Subjects and data collection*

We initially evaluated 194 consecutive patients who entered the Cardiology Clinic at our hospital with an acute coronary event over a period of 48 months. Only patients with a discharge diagnosis of acute coronary syndrome (ACS), acute myocardial infarction (MI) or unstable angina (UA) were included. The criteria for the diagnosis of STEMI, non-ST-segment elevation MI (NSTEMI) and (UA), were clinical evaluation, electrocardiographic findings and serum levels of the biochemical marker for myocardial necrosis. MI, in particular, was defined according to the latest guidelines, while UA was defined by the occurrence of one or more angina episodes, at rest, within the preceding 48-hours, corresponding to class III of the Braunwald classification [7, 8].

We measured serum potassium and glucose levels in all patients on admission and 2, 3, 6, 12, 24, 36 and 48 hours afterwards. All patients were monitored for supraventricular or ventricular arrhythmia. In this study, we enrolled only those patients who exhibited at least one episode of severe ventricular arrhythmia (sustained ventricular tachycardia or ventricular fibrillation) during the first 24 hours of hospitalization.

Information was obtained about patients' sociodemographic characteristics (e.g., age, sex, years of schooling, body mass index) and smoking habits. We also recorded patients' medical history, including previous hospitalization for cardiovascular disease (i.e. coronary heart disease, stroke or other cardiovascular disease), hypertension (medical records showing blood pressure greater or equal to 140/90 mmHg or use of anti-hypertensive drugs), hypercholesterolemia (medical records showing total serum cholesterol greater than 200 mg/dl or use of lipid lowering agents) and diabetes mellitus (use of anti-diabetic medication or blood glucose greater than 125 mg/dl) and family medical history. We recorded troponin I and the MB fraction of creatine kinase levels (CK-MB), creatinine, total serum cholesterol and blood pressure levels at the time of admission as well as interventional procedures and in-hospital outcome.

Renal insufficiency was initially quantified by the estimated creatinine clearance rate at baseline (CrCl). Based on baseline serum creatinine (Cr), CrCl was calculated using the Cockcroft-Gault formula: $CrCl = ((140 - age) \times weight) / (72 \times serum\ creatinine)$ for men, while for women, the results of the above equation were multiplied by 0.85 [9].

The study was approved by the Medical Research Ethics Committee at our institution and was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

*Data analysis*

Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are presented as absolute (relative, %) frequencies. Comparisons between continuous variables were performed using the Mann-Whitney non-parametric criteria, while associations between categorical variables were performed using the chi-square test. Repeated measures analysis of variance for ranked variables assessed the differences between potassium and glucose levels over time. The statistical analysis applied was RMANOVA. SPSS version 14 was used for all statistical calculations (SPSS Inc., Chicago, Illinois, USA).

## Results

We finally studied 162 patients (26% female) with acute coronary syndrome who exhibited at least one episode of sustained ventricular tachycardia/fibrillation during the first 24 hours of hospitalization. 53% were diagnosed as having STEMI and the remainder with NSTEMI. 47% of those with MI presented with anterior myocardial infarction. Of those admitted with STEMI, 31% received thrombolytic therapy. 132 of our patients (81.5%) were under optimal b-blocker treatment, while 47 (29.1%) received amiodarone and 20 (12%) were given xylocaine treatment. In 49 patients (30%), cardiac resychronisation therapy was applied. The remaining medications given were aspirin (90.7%), statins (78.4%), renin-angiotensin (RAAS) antagonists (68.5%) and clopidogrel (52.4%).

During hospitalization, 12% of males and 21% of females died ($p = 0.12$). The overall death rate was

 

14.2%. Those who died were older (70 ± 12 vs. 65 ± 12 years old, p = 0.05), more likely to have diabetes mellitus (48% vs. 27%, p = 0.04), more obese (43% vs. 20%, p= 0, 02) and less likely to have inferior infarction (9% vs. 11%, p = 0.01). No difference was found in the prevalence of thrombolytic therapy among the deceased and survivors (Table 1).

**Table 1.** Patients' characteristics according to in-hospital mortality

| Characteristic | Survived (n = 139) | Deceased (n = 23) | p |
|---|---|---|---|
| Age (yr) | 65 ± 12 | 70 ± 12 | 0.05 |
| Males (%) | 77 | 60 | ns |
| Diabetes (%) | 27 | 48 | 0.04 |
| Hypertension (%) | 38 | 26 | ns |
| Dyslipidemia (%) | 65 | 74 | ns |
| Obesity (%) | 20 | 43 | 0.02 |
| Smoking (%) | 52 | 57 | ns |
| Creatinine clearance (ml/min) | 69 ± 21 | 80 ± 33 | ns |
| LV ejection function (%) | 44 | 38 | 0.002 |
| Three-vessel disease (%) | 16 | 18 | ns |

**Legend:** Data are mean ± SD or percentage. LV: left ventricular.

Serum glucose levels at the onset of the arrhythmia, as well as after 2, 12, 36 and 48 hours, were higher in the deceased compared to survivors (onset: 228.8 ± 108 vs. 158 ± 68 mg/dl, p = 0.0001, 2 h: 182 ± 109 vs. 149 ± 59 mg/dl, p = 0.03, 12 h: 155.5 ± 72 vs. 128 ± 48 mg/dl, p = 0.025, 36 h: 163.8 ± 63 vs. 116 ± 42 mg/dl, p = 0.002, and 48 h: 138 ± 64 vs. 122 ± 42 mg/dl, p = 0.05, respectively). Further data analysis revealed that serum glucose levels measured at the onset of arrhythmia and 2, 36 and 48 hours later were still associated with in-hospital mortality, even after adjustment for age, sex, diabetes, creatinine clearance, type of acute coronary syndrome, site of infarction and medication administered including thrombolytic and antiarrhythmic treatment (p = 0.07). Similar findings were observed in the distribution of glucose levels between the deceased and survivors, when we stratified our analysis by diabetes status (p for interaction between outcome and diabetes status = 0.80). No differences were observed between diabetic and non-diabetic patients as regards ejection fraction (42% ± 8% vs. 43% ± 8%, p = 0.49). Serum potassium levels did not differ between those the deceased and survivors (p = 0.71; Table 2).

## Discussion

Diabetes mellitus is one of the major predictors of mortality in patients presenting with ACS [10, 11]. This is mainly attributed to the fact that diabetes has a deleterious effect on vascular function, thereby increasing the potential for coronary vasoconstriction and thrombosis. Furthermore, hyperglycemia has been associated with increased in-hospital mortality and congestive heart failure in patients hospitalized with acute MI [12], while in patients with ACS, hyperglycemia on admission represents an independent risk factor for short and long-term mortality, regardless of diabetes status [13-15]. In our study, we observed that higher serum glucose levels after ventricular tachycardia during the first 24 hours of hospitalization for an acute coronary event were associated with adverse in-hospital outcome.

In the DECODE study published in 2003, the hazard ratio for cardiovascular mortality increased progressively above a fasting plasma glucose level of 83 mg/dl and increased continuously in relation to increases in 2 h postprandial glucose levels [16, 17]. Relatively small increases in fasting and postprandial glucose levels (including impaired fasting glucose or impaired glucose tolerance) conferred an increased risk for cardiovascular morbidity and mortality. Putative mechanisms underlying the association between elevated glucose concentrations in the nondiabetic range, atherosclerosis and arrhythmogenesis include low density lipoprotein oxidation, haemostatic factors, advanced glycation end product formation on the vessel walls, increased endothelin 1 and inflammatory factors [18].

In our study, patients hospitalized with an acute coronary event who exhibited severe ventricular arrhythmia, presented serum glucose levels at the onset of the arrhythmia and 2, 36 and 48 hours later, which had prognostic significance for in-hospital mortality. The role of admission hyperglycemia has been evaluated in other studies. Pertusson *et al.*, revealed that even among patients without diabetes, those with hyperglycemia had a higher 30-day and late mortality rate [19]. Timmer *et al.* reached the same conclusion, suggesting that elevated admission glucose appears to be more important than prior long-term abnormal glucose metabolism in predicting mortality in patients with acute coronary syndrome [20]. Furthermore,

**Table 2.** Patients' potassium and glucose levels according to in-hospital mortality

| Potassium, Glucose | Survived (n = 139) | Deceased (n = 23) | p |
|---|---|---|---|
| Potassium (mg/dl) | | | |
| 0 h | 4.08 ± 0.5 | 4.10 ± 0.6 | ns |
| 2 h | 4.13 ± 0.4 | 4.06 ± 0.5 | ns |
| 4 h | 4.14 ± 0.3 | 4.08 ± 0.4 | ns |
| 6 h | 4.16 ± 0.4 | 4.11 ± 0.4 | ns |
| 12 h | 4.18 ± 0.4 | 4.20 ± 0.6 | ns |
| 24 h | 4.21 ± 0.5 | 4.15 ± 0.5 | ns |
| 36 h | 4.21 ± 0.4 | 4.30 ± 0.6 | ns |
| 48 h | 4.29 ± 0.4 | 4.51 ± 0.5 | 0.06 |
| Glucose (mg/dl) | | | |
| 0 h | 157.68 ± 68.5 | 228.78 ± 108.5 | < 0.001 |
| 2 h | 149.20 ± 59.0 | 182.43 ± 109.3 | 0.03 |
| 4 h | 139.50 ± 47.0 | 175.66 ± 85.0 | 0.004 |
| 6 h | 137.70 ± 54.6 | 172.90 ± 82.6 | 0.01 |
| 12 h | 128.30 ± 47.7 | 155.48 ± 71.5 | 0.02 |
| 24 h | 124.30 ± 51.1 | 150.77 ± 69.6 | 0.03 |
| 36 h | 116.30 ± 41.9 | 163.80 ± 63.4 | 0.02 |
| 48 h | 122.05 ± 42.0 | 138.11 ± 63.7 | 0.05 |

**Legend:** Data are mean ± SD.

Barsheshet *et al*., revealed in a recent study that mortality risk correlated with admission glucose levels. Each 18-mg/dl increase in glucose level was associated with a 31% increased risk of in-hospital mortality and a 12% increase in 60-day mortality [21]. In a meta-analysis of 15 relatively small and generally older studies, which evaluated the association between admission glucose level and mortality, Capes *et al*. [22] demonstrated that the relative risk of in-hospital death in nondiabetic patients with acute myocardial infarction and admission glucose of 110 mg/dl was 3.9 compared to nondiabetic, normoglycemic patients. Furthermore, among diabetic patients with myocardial infarction, those with admission glucose above 180 mg/dl had a 70% relative increase in the risk of in-hospital death compared with diabetic patients with normal admission glucose values.

We evaluated the impact of serum glucose levels on in-hospital mortality in patients who developed sustained ventricular tachycardia or ventricular fibrillation. In general, the appearance of ventricular tachycardia during hospitalization for ACS has been related to the extent of the myocardial infarction and the progression of left ventricular remodeling. Altered left ventricular architecture and function during post-infarction left ventricular remodeling provide an important substrate for triggering high-grade ventricular arrhythmias [6]. Previous studies have revealed that the presence of diabetes mellitus is associated with larger infarct size, measured by nuclear imaging techniques, which is attributed to more extensive coronary artery disease, impairment of collateral recruitment and poorer restoration of tissue perfusion as compared with non-diabetic patients [23, 24]. This may explain the higher prevalence of ventricular tachycardia observed in patients with impaired glucose levels. Furthermore, hyperglycemia is associated with elevated systolic and diastolic blood pressures and QT prolongation, changes that are alleviated when hyperglycemia is corrected [25].

A possible explanation for the higher in-hospital mortality observed in patients with higher glucose levels on admission and after an episode of ventricular tachycardia, may be the deleterious effects of hyperglycemia on arrhythmia and ischemia incidence. Higher glucose levels in patients with acute coronary syndrome have been associated with higher free fatty acid concentrations, insulin resistance, and impaired myocardial glucose utilization. All these metabolic situations increase oxygen consumption and potentially worsen ischemia. Higher free fatty acid concentrations in turn have been linked to an increased incidence of malignant ventricular arrhythmias [26, 27]. On the other hand, hypoglycemia on admission was associated with increased risk of "hard events" at 30 days. It seems that both low and high serum glucose values are related to adverse cardiac events [28]. Given the multiple detrimental effects of elevated glucose levels on the cardiovascular system, it is possible that poor glucose control during hospitalization may have a direct effect on outcomes in patients hospitalized with acute coronary syndrome.

Our study revealed that the first 36 hours in particular after initiation of severe ventricular arrhythmia in patients hospitalized for an acute coronary event, represent a critical period of vulnerability to hyperglycemia with adverse clinical outcome. The limitation of the present study is that several biochemical markers, including hemoglobin, myocardial necrosis enzymes and inflammatory markers, have not been evaluated.

## Conclusion

Several studies have been conducted to determine the role diabetes plays in the prognosis of patients after acute myocardial infarction and treatment with fibri-

 

nolytic agents. They have demonstrated that diabetes remains a major risk factor for poor short and long-term outcome even after thrombolytic therapy. In this study, we revealed the prognostic significance for in-hospital mortality of serum glucose levels at the onset of arrhythmia and 2, 36 and 48 hours later in patients hospitalized for an acute coronary event, who exhibited severe ventricular tachycardia.

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