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Serum calcium levels independently predict in-hospital mortality in patients with acute myocardial infarction

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Abstract *Background and aim:* Serum calcium levels (sCa) were reported to be associated with cardiovascular risk factors, incidence of coronary artery disease and acute myocardial infarction (AMI). The current study evaluated the association between sCa and in-hospital mortality among AMI patients.
Methods and results: Patients admitted in a tertiary medical center for AMI throughout 2002–2012 were analyzed. For each patient, mean sCa, corrected to albumin, was calculated and categorized to seven equally-sized groups: <8.9, 8.9–9.12, 9.12–9.3, 9.3–9.44, 9.44–9.62, 9.62–9.86, ≥9.86 mg/dL. The primary outcome was all-cause in-hospital mortality. Out of 12,121 AMI patients, 11,446 were included, mean age 67.1 ± 14 years, 68% Males. Mean number of sCa values for patient was 4.2 ± 7.3. Mean sCa was 9.4 ± 0.53 mg/dL, range 5.6–13.2 mg/dL sCa was significantly associated with cardiovascular risk-factors, in-hospital complications, more frequent 3-vessel coronary artery disease and decreased rate of revascularization, often in a U-shaped association. Overall 794 (6.9%) patients died in-hospital. Multivariate analysis showed a significant U-shaped association between sCa and in-hospital mortality with sCa below 9.12 mg/dL and above 9.86 mg/dL as independent predictors of significantly increased in-hospital mortality: OR = 2.4 (95% CI:1.7–3.3) and 1.7 (95%CI:1.2–2.4), for Ca<8.9 and Ca≥9.86 mg/dL respectively $p < 0.01$, as compared with middle rage sCa group (9.3–9.44 mg/dL).
Conclusion: sCa is an independent predictor of in-hospital mortality in patients with AMI with a U-shaped association. Both increased and decreased sCa levels are associated with increased risk of in-hospital mortality.

Introduction

Risk stratification after acute myocardial infarction (AMI) is of great importance for prudent therapeutic decision-making. Calcium is the most abundant mineral in the human body [1]. While most of the body's calcium is sequestered in the skeleton, the free, hydrated cation is a key physiologic mediator in a host of metabolic and regulatory processes [1]; impacting cardiovascular disease: platelet adhesion, blood coagulation, cardiac contraction, cardiomyocyte apoptosis and electrophysiology [2,3]. Serum calcium levels (sCa) has been previously reported to be associated with cardiovascular risk factors such as hypertension, dyslipidemia, blood glucose abnormalities,

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body mass index and smoking as well an independent predictor of the incidence of coronary artery disease (CAD) and AMI [4–6]. Furthermore, sCa was associated with risk of total, cardiovascular, and non-cardiovascular mortality in the community [7] and all-cause mortality in patients with stable CAD [8] as well as in critically ill patients [9]. A consistent adverse trend in the risk of AMI has been shown with calcium supplements [10,11]. Similarly, a U-shaped association between dietary calcium intake and cardiovascular mortality was reported [10]. Lu et al. [12] recently evaluated calcium level as a prognostic marker following AMI and reported that lower calcium levels are an independent predictor for in-hospital mortality in patients (1,431) with ST-elevation MI (STEMI). Similarly, Yan et al. [13] showed that a decreased baseline sCa is an independent predictor of the in-hospital mortality, weakly correlated with the GRACE risk score and added incremental predictive value when combined with the GRACE score in patients (n = 1431) with acute coronary syndrome. Although increased sCa have been reported to be a significant predictor of AMI [4,6,14] and cardiovascular mortality in the community [7,15,16], they have not been shown to impact outcome in the studies of Lu and Yan [12,13], as reported above. Hence, studies evaluating sCa as an independent prognostic marker for mortality in AMI patients are scarce and when exist, are possibly too small to extensively uncover the true associations. The aim of the current study was to evaluate the association between sCa and in-hospital mortality in a contemporary large "real life" cohort of patients with AMI.

Methods

Study population

In this retrospective study we reviewed the medical records of consecutive AMI patients who were admitted to Soroka University Medical Center (SUMC) with a recorded diagnosis of AMI throughout 2002–2012. SUMC is a tertiary referral center (1200 beds), serving the southern Israel region. Exclusion criteria were: chronic renal replacement therapy (dialysis), missing sCa or albumin values.

The local ethics committee approved the study, which was performed in accordance with the Helsinki declaration.

Data sources and classifications

Data were obtained from the hospital's computerized medical records. The data included demographic and clinical characteristics, cardiovascular risk factors and co-morbidity, clinical workup (e.g. blood tests, echocardiography and coronary angiography) and interventions administered for the AMI, Mortality data were obtained from the Ministry of the Interior Population Registry.

As previously reported [17], AMI diagnosis was identified based on the international Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes: ST-elevation AMI (STEMI): 410.0*- 410.6* and Non-ST-elevation AMI (NSTEMI): 410.7*-410.9*. Grouping of diseases and interventions were based on ICD-9-CM discharge codes.

The sCa levels were routinely collected during patients' hospitalization and analyzed using a photometric color test for clinical chemistry analyzers (Olympus System Reagent; Olympus Diagnostica). For the study purposes, sCa levels (mg/dL) were corrected to albumin (g/dL) levels, from the same sample, according to the Payne formula [18]: corrected sCa = Ca + 0.8 X (4.0 − albumin). All Calcium concentrations presented in the current manuscript are corrected for albumin and referred to as sCa.

For each patient, mean sCa, corrected to albumin, was calculated and categorized to seven equally-sized groups: <8.9, 8.9–9.12, 9.12–9.3, 9.3–9.44, 9.44–9.62, 9.62–9.86 and ≥ 9.86 mg/dL.

Outcomes

The primary outcome was in hospital all-cause mortality.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 24 software. Patient characteristics were presented as mean and standard deviation (SD) for continuous variables and n and percent for the categorical data. The comparison of baseline characteristics between the sCa groups was performed using Chi-square and Analysis of variance (ANOVA) tests. The comparison of the outcome between the study groups was performed using Chi-square test. In addition, logistic regression analysis was performed in univariate and multivariate levels in order to estimate the relative risk (Odds Ratio − OR) for mortality for the study groups. In this analysis, the group of the middle sCa level (9.3–9.44 mg/dL) served as the reference group. Multivariate regression model included the investigated baseline characteristics which were statistically related to the outcome. For each test, $P < 0.05$ was considered as statistically significant.

The non-linearity of the association between sCa level and mortality were evaluated by comparison between two models of logistic regression. In the first, "linear" model the association between categories of sCa levels (increase in sCa level category) and mortality was assessed. In the second, "polynomial" model, sCa as a categorized variable, was transformed calculating square root. Furthermore, we evaluated the impact of adding sCa (linear vs. root square) to the models, using Omnibus Tests of Models Coefficients.

Results

The initial cohort included 12,121 AMI patients, following exclusion of 675 (5.6%) patients (3.56% were on dialysis, 3.9% and 5% did not have available sCa or albumin levels, respectively) 11,446 were analyzed in the current study. The mean age of the study cohort was 67.1 years (SD = 14.1), 68.1% Males, 24.8% minorities (Bedouins). sCa levels among the study cohort ranged between 5.6 and

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