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Brief report

Glycated hemoglobin in ST-elevation myocardial infarction without previously known diabetes: Its short and long term prognostic role

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ABSTRACT

In 518 consecutive STEMI non-diabetic patients, glycated hemoglobin > 6.5% was not associated with increased short and long term mortality, but was associated with higher admission glucose values, worse in-hospital glycemic control and a higher incidence of acute insulin resistance (HOMA index).

1. Introduction

Data on the prognostic role of glycated hemoglobin (HbA1c) in patients with acute myocardial infarction are still controversial [1–9].

We assessed the prognostic role of HbA1c for short and long term mortality in 518 consecutive patients with ST elevation myocardial infarction (STEMI) and without previously known diabetes. All were treated with mechanical revascularization.

2. Methods

From 1st January 2008 to 30th June 2010, 518 non-diabetic STEMI patients (within 12 h from symptoms' onset) were admitted to our Intensive Cardiac Care Unit (ICCU) [10–14]. Renal replacement therapy and mechanical ventilation were used, when needed [10–13]. After PCI, fasting glucose, insulin [12,13], C-peptide, HbA1c, troponin I, uric acid, C-reactive protein, alanine aminotransferase (ALT), aspartate amino transferase (AST) [15], gammaglutamyl transferase (GGT) [16], NT-pro Brain Natriuretic Peptide (NT-pro BNP) [13], total cholesterol, triglycerides, HDL, fibrinogen and creatinine were measured. Glomerular filtration rate (1 ml/min/1.73 m^2) was calculated [17] as well as LDL (nv 60–190). Peak glucose, peak Tn I and nadir glomerular filtration rate were also measured. Insulin resistance was defined by the Homeostatic Model Assessment (HOMA). HOMA was calculated according to the following formula: {[fasting insulin (microU/ml)] × [fasting glucose (mmol/l)]}/22.5 [27]. Subjects whose values exceeded the sex-specific 75th

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percentile (i.e. 1.80 for women and 2.12 for men) were considered to have insulin resistance (HOMA-IR) [11,12,18].

The study protocol was in accordance with the Declaration of Helsinki and approved by the local Ethics Committee. Informed consent was obtained in all patients before enrolment.

3. Statistical analysis

Data are reported as frequencies (percentages) and medians (95% Confidence Interval – CI) and analyzed by means of χ^2 (or Fisher's exact text, when predicted counts in almost one cell were less than 5) for categorical variables and Mann–Whitney *U*-test for continuous variables (which, at Kolmogorov–Smirnov normality test, were almost all non-normally distributed), respectively. In-ICCU mortality was assessed by logistic regression; a univariant analysis identified parameters that were significantly associated with outcome and these were used as candidate variables in a multivariant logistic regression model. Nagelkerke pseudo-R^2 and Hosmer–Lemeshow goodness-of-fit analyses are reported. Since the multivariable model was slightly overfitted, due to the low number of events, the data was further assessed by plotting a receiver operating characteristic (ROC) curve with each patient's estimated probability of death, in order to determine the discrimination achieved by the area under the curve (AUC). Long time survival was explored by means of Kaplan–Meier analysis with respect to HbA1c as a dichotomous variable (Log-rank test has been reported), as well as, after proportionality of risk assessment with Cox regression analysis, in both a univariant and multivariant manner. In this latter analysis, variables for inclusion were carefully chosen, given the number of events available, to ensure parsimony of the final model; non-significant variables were dropped by means of backward selection. Dichotomous HbA1c was forced into the analyses. A p value <0.05 was considered statistically significant (SPSS 13.0; SPSS Inc., Chicago, IL).

4. Results

Patients with HbA1c $\geq$ 6.5% showed higher values of admission, peak and discharge glucose ($p < 0.001$, <0.001 and <0.001, respectively) and a higher incidence of HOMA positivity ($p = 0.001$) as well as higher values of ESR ($p < 0.001$), fibrinogen ($p < 0.001$) and triglycerides ($p = 0.001$) and lower values of HDL ($p = 0.018$). There were no differences in short and long-term mortality rates or in the use of devices. Independent predictors for in-hospital mortality were (multivariate backward logistic regression analysis): admission glycemia (OR: 3.95, 95%CI: 1.92–8.12, $p < 0.001$), eGFR (1 ml/min/1.73 m^2 increase) (OR: 0.96, 95%CI: 0.93–0.98, $p = 0.002$), peak Tn I (10 ng/ml increase) (OR: 1.03, 95%CI: 1.01–1.06, $p = 0.088$). Hosmer and Lemeshow test $\chi^2 = 2.58$, $p = 0.589$; Nagelkerke $R^2 = 0.46$; area under the ROC curve 93% (95%CI: 88–99%, $p < 0.001$). HbA1c was not associated with in-hospital death (OR: 7.21, 95%CI: 0.75–69.69, $p = 0.088$). At follow-up (median of 39.7 months (22.2–57.1)), the Kaplan–Meier survival curve showed no significant differences between patients with HbA1c <6.5% and those with ≥6.5%. Table 1 shows the Cox regression analysis for long term mortality.

Table 1 – Adjusted Cox regression analysis.

	HR	95%CI	p	Wald
Age (1 year step)	1.054	1.018–1.092	0.003	8.828
Discharge LVEF (1% step)	0.951	0.914–0.990	0.014	6.028
Nadir eGFR (1 ml/min/1.73 m^2 step)	0.981	0.963–0.999	0.045	4.023
HbA1c >6.5%	0.705	0.213–2.338	0.568	0.326

LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate.

5. Discussion

In patients without a history of diabetes, only small studies on the prognostic role of HbA1c with different methods and results exist [6–9]. In 150 non-diabetic patients with MI, mortality rate and the risk of cardiogenic shock increased with HbA1c [6]. In a high-risk MI population [8] HbA1c was a risk marker of death at follow-up in patients without a history of diabetes and not in diabetic patients. In a small group of MI patients (diabetic and non-diabetic) treated with thrombolysis [7], there were significant relationships between admission glucose, HbA1c level and mortality at follow-up. Conversely, in 504 unselected, consecutive non-diabetic STEMI patients submitted to PCI, hyperglycemia (not glycated hemoglobin) was a predictor of 30-day outcome [9]. The main finding of our investigation is that HbA1c values were not related to mortality, short and long term, in consecutive STEMI patients without previously known diabetes, who were submitted to mechanical revascularization. In our investigation, patients with HbA1c levels higher than 6.5% did not show a higher infarct size (as indicated by Tn I and left ventricular ejection fraction) or a more critically illness (as inferred by the use of devices). Discrepancies with previous papers are mainly related to number consistency [6], population selection criteria [7] and type of revascularization [9]. Different from previous studies [6–9], we observed for the first time that higher HbA1c values helps in identifying a subset of patients who, in the early phase of STEMI, show an abnormal glucose response to stress as indicated by higher values of glucose, worse glycemic control during ICCU stay (peak glycemia) and a higher incidence of acute insulin resistance (HOMA index). All these factors have been associated with increased risk of early death by others [19] and us [10–12,18,20].

Patients with HbA1c > 6.5% also showed a increased inflammatory activation (increased values of fibrinogen and ESR), suggesting a link between acute glucose dysmetabolism and inflammation in the early phase of STEMI [19,20].

In conclusion, though increased values of HbA1c are not associated with a worse prognosis, non-diabetic STEMI patients with HbA1c > 6.5% may merit closer attention to in-hospital glucose management, since they exhibit an abnormal glucose response to stress.

Conflict of interest

The authors declare that they have no conflict of interest.

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