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Glycosylated hemoglobin is associated with decreased endothelial function, high inflammatory response, and adverse clinical outcome in non-diabetic STEMI patients

Filipe A. Moura [a], Valeria N. Figueiredo [a], Bruna S.B.S. Teles [b], Meyrianne A. Barbosa [b], Lara R. Pereira [b], Ana P.R. Costa [b], Luiz Sergio F. Carvalho [a], Riobaldo M.R. Cintra [a], Osório L.R. Almeida [c], Jose C. Quinaglia e Silva [c], Wilson Nadruz Junior [a], Andrei C. Sposito [a, *], on behalfof Brasilia Heart Study

[a] State University of Campinas Medicine School (UNICAMP), Campinas, SP, Brazil
[b] University of Brasilia Medical School (UnB), Brasilia, Brazil
[c] Hospital de Base do Distrito Federal, Brasilia, DF, Brazil

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ABSTRACT

Objective: Chronic dysglycemia was recently identified as a predictor for adverse outcomes in patients with ST-elevation myocardial infarction (STEMI) treated by percutaneous coronary intervention. Data for non-diabetic patients who underwent thrombolysis is scarce. In this context, we aimed to study the effect of HbA1c on cardiovascular outcome after STEMI.

Methods: A prospective cohort of 326 non-diabetic STEMI individuals was used for the analyses. We measured plasma glucose, hemoglobin A_{1c} [HbA_{1c}], lipid profile, C-reactive protein (CRP), and nitrate/nitrite (NOx) upon admission and five days after STEMI (D5). Flow-mediated dilation (FMD) was performed 30 days after STEMI. During clinical follow-up, we assessed patients for incident diabetes (progression to HbA1c $\geq$ 6.5%) and major adverse cardiac events (MACE), defined as a composite of fatal and non-fatal MI, sudden cardiac death, and angina requiring hospitalization.

Results: Using ROC-curve analysis, a 5.8% HbA1c best predicted MACE with a sensitivity of 75% and specificity of 53% (AUC 0.673, $p = 0.001$). Patients were categorized as high HbA1c if $\geq$ 5.8% and low HbA1c if <5.8%. Compared with patients with low HbA1c, those with high HbA1c presented with 20% higher CRP-D5 ($p = 0.009$) and 19% higher ΔCRP ($p = 0.01$), a 32% decrease in ΔNOx ($p < 0.001$), and 33% lower FMD ($p < 0.001$). After a median follow-up of 1.9 (1.1–2.8) years, patients with high HbA_{1c} had more incident diabetes (HR 2.3 95% CI 1.01–5.2; $p = 0.048$) and MACE (HR 3.32 95% CI 1.09–10.03; $p = 0.03$).

Conclusion: Non-diabetic STEMI patients with high HbA_{1c} present with decreased endothelial function and increased inflammatory response and long-term risk of MACE.

1. Introduction

Hyperglycemia on admission is an established independent prognostic marker in myocardial infarction patients (MI) with or without diabetes mellitus [1,2]. This may be explained by the fact that hyperglycemia predisposes to thrombus formation, endothelial dysfunction, oxidative stress, and increased inflammatory activity [3]. In contrast, the role of chronic glucometabolic status prior to MI in predicting outcome is less clear. In a recent study, admission glycosylated hemoglobin (HbA_{1c}) was shown to be directly related to mortality after 3.3 ± 1.5 years of follow-up in non-diabetic patients with ST-segment elevation MI (STEMI) that were treated with primary percutaneous coronary intervention (PCI) [4]. However, this evidence cannot be extrapolated to a considerable proportion of STEMI patients around the world, who are still substantially treated with thrombolytics [5–9]. For example, in

* Corresponding author. Laboratory of Atherosclerosis and Vascular Biology (AteroLab), Cardiology Division, State University of Campinas Medicine School (Unicamp), 13084-971, Campinas, Sao Paulo, Brazil.
E-mail address: andreisposito@gmail.com (A.C. Sposito).

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contrast to patients treated with primary PCI, those undergoing thrombolytic therapy are prone to having a larger MI mass, worse coronary residual perfusion, and higher incidence of re-occlusion of the infarct-related artery [10].

Besides the aforementioned mechanisms that may influence the PCI-related outcome, there are additional processes that may underlie the association between HbA_{1c} and mortality such as: increased thrombogenesis [11], impaired plasmin activation due to enhanced levels of plasminogen activator inhibitor 1 [12], extent of ischemia-reperfusion injury [13], and endothelial dysfunction [14]. Hence, the assumption of a direct association between HbA_{1c} and mortality in non-diabetic patients with STEMI not treated mainly by PCI deserves a proper investigation.

When evaluating HbA1c levels, it is important to consider possible confounding lifestyle habits that may affect both HbA1c and cardiovascular risk. Thus, it is appropriate to monitor STEMI patients for potential confounders that are associated with HbA1c status such as nutritional behavior. Adjustments for this potential confounder have not been done in previous studies. Thus, we aimed to verify the effect of HbA1c on outcome in this particular setting using a study that was designed to control for lifestyle habits.

2. Materials and methods

2.1. Study patients

The *Brasilia Heart Study* (ClinicalTrials.gov Identifier: NCT02062554) is an ongoing prospective observational cohort of STEMI patients admitted to Hospital de Base do Distrito Federal, which is a referral center for acute coronary syndromes in Brasilia, Brazil [15]. The study's flow diagram is depicted in Fig. 1. Enrollment took place between May 2006 and December 2013 and eligibility criteria for participants were as follows: (i) less than 24 h after the onset of MI symptoms, (ii) ST-segment elevation of a least 1 mm (frontal plane) or 2 mm (horizontal plane) in two contiguous leads, (iii) myocardial necrosis as evidenced by an increase to at least one value above the 99th percentile above the reference limit of CK-MB (*i.e.* 25 U/L) and troponin I (*i.e.* 0.04 ng/mL) followed by a decline of both, and (iv) absence of impediments for clinical follow-up. Cohort individuals with a previous diagnosis of diabetes, reported use of hypoglycemic agents, or with $HbA_{1c} \geq 6.5\%$ were classified as having type 2 diabetes and excluded from the analysis of the current study. The local Ethics Committee approved the study and all patients signed an informed consent. The authors had full access to the data and vouch for its integrity and analysis as well as to the contents of the manuscript.

2.2. In-hospital evaluation

A complete medical evaluation and a food frequency questionnaire were performed on all patients on day one of hospital admission (D1). Admission data is later used to determine risk using scores such as the global registry of acute coronary events (GRACE) risk score [16], which estimates the 6-month risk of death. Medical treatment during hospitalization was decided by the attending physician without the interference of the researchers and followed a protocol based on the current ACC/AHA guidelines for STEMI. Blood samples were drawn from every patient on D1 and after a 10 h overnight fast five days after MI (D5) and centrifuged for 10 min at 3500 rpm. Plasma was aliquoted and stored at −80 °C for later appraisal.

2.3. Biochemical analysis

The following measurements were performed: glucose (Glucose GOD-PAP, Roche Diagnostics, Mannheim, Germany), total cholesterol (CHOD-PAP, Roche Diagnostics, Mannheim, Germany), triglycerides (GPO-PAP, Roche Diagnostics, Mannheim, Germany), high-density lipoprotein cholesterol (HDL-C) (Roche Diagnostics, Mannheim, Germany), C-reactive protein (CRP), and HbA_{1c} (Variant II, Bio-Rad Laboratories, Hercules, CA, USA). The value of low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula. Nitrite and nitrate (NOx) levels were determined by a nitric oxide chemiluminescence analyzer (model NOA, Sievers Instruments, Boulder, CO) after reduction with acidic vanadium (III) chloride.

2.4. Dietary evaluation

Dietary caloric intake and composition were assessed using the food frequency questionnaire (Supplements). The questionnaire estimated dietary intake of 62 food items divided into ten groups (eggs and meat, oils, snacks, canned goods, milk products, cereals and legumes, vegetables and fruits, desserts and sweets, beverages, spices, and diet and light products) over the previous 90 days. The food proportions in household measures were standardized with the help of a photographic record for dietary inquiries, and the portion sizes were transformed into weights. Dietary intake of carbohydrates and lipids were quantified according to the validated Brazilian Table of Food Composition – version 2 [17,18] by an experienced nutritionist who was blinded to all laboratory and clinical data. The dietary composition values were blinded to all other study participants.

2.5. Coronary angiography

Coronary angiography was systematically performed on all patients enrolled into the study in accordance with standard techniques. Luminal narrowing ≥50% of left main coronary or right coronary artery or ≥70% of all other vessels was considered significant stenosis. Coronary disease severity was estimated by the SYNTAX score. Thrombolysis In Myocardial Infarction (TIMI) flow grade and Myocardial Blush Grade (MBG) were assessed after angioplasty in patients who underwent primary PCI or at the first angiogram performed on the fifth to seventh day after thrombolysis.

2.6. Cardiac magnetic resonance imaging (CMRI)

In a subgroup of 84 patients, CMRI studies were carried out 30 days after MI (D30) using a MRI scanner with a 1.5-T (Signa CV/i, GE Medical Systems, Waukesha, WI) which was equipped with a gradient of high performance (gradient strength 40 mT/m; maximum slew rate 150 mT/m/s) and a four elements phased array cardiac coil. The area of MI extent was quantified using the gadolinium-based delayed enhancement of myocardial images. On cine-CMRI, end-systolic and end-diastolic left atrium and left ventricle volumes as well as ejection fraction were measured by ReportCard software (GE Medical Systems, Waukesha, WI), applying Simpson's method [19].

2.7. Brachial artery reactivity

Brachial artery reactivity was systematically assessed 30 days (D30) after STEMI to estimate the decline in endothelial function persistent after the acute phase stress. At the time of the measurement, all patients were medicated according to secondary prevention protocol (described below) for at least 3 weeks. Brachial artery measurements were performed after overnight fasting and vasoactive medications were withdrawn 24 h before assessment. After