International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Adverse outcome has a U-shaped relation with acute phase change in insulin sensitivity after ST-Elevation Myocardial Infarction

Filipe A. Moura [a], Riobaldo Cintra [a], Luiz S.F. Carvalho [a], Simone N. Santos [a], Rodrigo Modolo [a], Daniel B. Munhoz [a], Jose Carlos Quinaglia e Silva [b], Otavio R. Coelho [a], Wilson Nadruz [a], Andrei C. Sposito [a,*,1]

[a] Cardiology Division, Faculty of Medical Sciences, State University of Campinas Medical School (Unicamp), Campinas, SP, Brazil
[b] Hospital de Base do Distrito Federal, Brasilia, DF, Brazil

ARTICLE INFO

Article history:
Received 3 February 2017
Received in revised form 19 July 2017
Accepted 30 November 2017
Available online xxxx

Keywords:
Insulin sensitivity
HOMA
Myocardial infarction
STEMI
Mortality

ABSTRACT

Background: Although stress hyperglycemia after myocardial infarction (MI) is consistently associated with increased mortality, recent studies suggest that the addition of upstream markers of glucose metabolism may improve risk identification. Hence, our aim was to evaluate the association between insulin sensitivity changes during MI hospitalization and outcomes.
Methods: A prospective cohort of 331 consecutive ST-Elevation MI (STEMI) patients without insulin provision therapy was used for the analyses. Blood samples were collected upon admission (D1) and after 5 days (D5) of the inciting event. We measured blood glucose and insulin to estimate insulin sensitivity using the updated Homeostasis Model Assessment (HOMA2S). Patients were assessed for intra-hospital death and major adverse cardiac events (MACE) during follow-up.
Results: HOMA2S was 62% ± 52% on D1 and 86% ± 57% on D5 ($p < 0.001$). Total follow-up was a median of 2 (0.9–2.8) years and found a U-shaped relation between the change in HOMA2S from D1 to D5 (ΔHOMA2S) and major adverse cardiac events (MACE) ($p = 0.017$). Fully adjusted cox-regression models showed that patients from T1 and T3 were about 2.5 times more prone to suffer from MACE than those in T2. Net Reclassification Index adding ΔHOMA2S as a categorical variable dichotomized as T2 and T1 or T3 to a model of GRACE risk score with glucose D1 yielded a better predictive model (0.184 [95% CI 0.124–0.264]; $p = 0.032$).
Conclusion: A U-shaped curve describes the relation between insulin sensitivity change and MACE during acute phase STEMI and, thus indicating that acute dysglycemia must be appreciated in light of a time spectrum and insulin levels.

1. Introduction

The incidence of stress hyperglycemia in patients admitted with myocardial infarction (MI) has doubled in the last 20 years, nowadays occurring in about half of patients [1]. The biggest concern with this trend lies in the fact that hyperglycemia during acute coronary syndromes (ACS) is associated with increased mortality at 30 days, 1 year, and even 20 years after the inciting event [1], [2]. Furthermore, this association exists in both diabetic and non-diabetic patients with MI [3].

From a pathophysiological standpoint, hyperglycemia can feasibly affect outcome by decreasing collateral circulation, endothelial function, and ischemic preconditioning [4]. It can also increase myocardial cell apoptosis, thrombogenicity, and systemic inflammatory activity [4]. The only existing randomized study with ACS patients to date in which the glucose level was significantly lowered in the intervention group suggests there may be a causal role between the reduction in blood glucose and reduced mortality [5]. On the other hand, the association between hyperglycemia and mortality persists even after controlling for comorbidities, severity of coronary disease, and residual ventricular dysfunction, which gives way to the possibility of an indirect association or an unexplored mechanism [6].

Although the actual contribution of hyperglycemia in MI remains unclear, there are particular features that stand out. First, pre-existing diabetes seems to mitigate the risk associated with hyperglycemia [2]. Second, the increase in blood glucose during the first days after MI has greater impact on prognosis than admission blood glucose [6]. Thirdly, the degree of insulin resistance estimated during MI is associated with early mortality regardless of admission glycemia [7]. Taking all this evidence under consideration, it is reasonable to infer that the temporal variation in ST-elevation MI (STEMI) -related insulin resistance may influence the adverse effects of stress hyperglycemia.

* Corresponding author at: Cardiology Division, Faculty of Medical Sciences, State University of Campinas (Unicamp), 13084-971 Campinas, SP, Brazil.
E-mail address: sposito@fcm.unicamp.br (A.C. Sposito).
[1] On behalf of the Brasília Heart Study Group.

https://doi.org/10.1016/j.ijcard.2017.11.111
0167-5273/

In order to assess insulin sensitivity in a larger number of STEMI patients, we conducted a preliminary study comparing surrogate insulin sensitivity indexes with the hyperinsulinemic euglycemic clamp in STEMI patients [8]. In this preliminary study, we found that the second version of the Homeostasis Model Assessment (HOMA2S) best estimates insulin sensitivity in these patients. In this context, the aim of the present study was primarily to both verify the existence of a change in insulin sensitivity, as measured by HOMA2S, during the acute phase of MI and its implications on clinical outcome. As secondary objectives, we sought to explore potential mechanisms that may mediate the association between dysglycemia and unfavorable clinical outcome.

2. Methods

2.1. Study patients

Study participants were from the *Brasilia Heart Study* [9] (ClinicalTrials.gov Identifier: NCT02062554). It is an ongoing observational prospective cohort of consecutive ST-elevation MI (STEMI) patients admitted to *Hospital de Base do Distrito Federal*, a reference hospital located in Brasilia, Brazil. The current study included 331 patients enrolled between May 2006 and December 2015 and the flow diagram is illustrated in Fig. 1. Inclusion criteria were as follows: (i) <24 h after the onset of MI symptoms, (ii) ST-segment elevation ≥ 1 mm (limb leads) or ≥2 mm (precordial leads) 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 (25 U/L) and troponin I (0.04 ng/mL) followed by a decline of both, (iv) and absence of hindrances for maintaining clinical follow-up. Individuals with previous use of insulin, insulin providers such as sulphonylureas or incretin-mimetic agents, i.e. dipeptidyl peptidase-4 inhibitors or glucagon-like peptide-1 agonists, were excluded from the study. The rationale behind this is because these represent an extremely heterogeneous population and these pharmacotherapies alter endogenous insulin levels and intrinsic IS, thus potentially directly interfering with the interpretation of our data.

Diabetes status was defined as previously diagnosed diabetes, use of hypoglycemic agents, or HbA1c ≥ 6.5%. In-hospital patient treatment was always conducted according to in-house assistant physicians and study investigators played a purely observational role. The physicians involved in the treatment of the patients were blind to all analyses performed in the study. The local Ethics Committee approved the study and all participants were required to sign an informed consent.

3. Biochemical analysis

Blood samples were obtained at D1, i.e. <24-h from MI onset, and at day five following MI (D5). Collected blood samples were centrifuged for 10 min at 3500 rpm and plasma was aliquoted for storage at −80 °C. The following biochemical panel was obtained from plasma samples and measured using standard laboratory methods: glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, and high-sensitivity C-reactive protein. HbA1c was measured using high-performance liquid chromatography. A NO chemiluminescence analyzer (model NOA, Sievers Instruments, Boulder, CO) was used to determine the plasma pool of nitrite and nitrate (NOx) after reduction with acidic vanadium (III) chloride. Plasma insulin and C-peptide concentrations were respectively assessed by electrochemiluminescence and imunoquimioluminescence. The Homeostasis Model Assessment version 2 (HOMA2) was used to estimate insulin sensitivity (HOMA2S) using fasting plasma insulin and glucose and calculator version 2.2 [10]. The validity of HOMA2 index during STEMI was previously verified in STEMI patients by euglycemic hyperinsulinemic clamp in our laboratory [8].

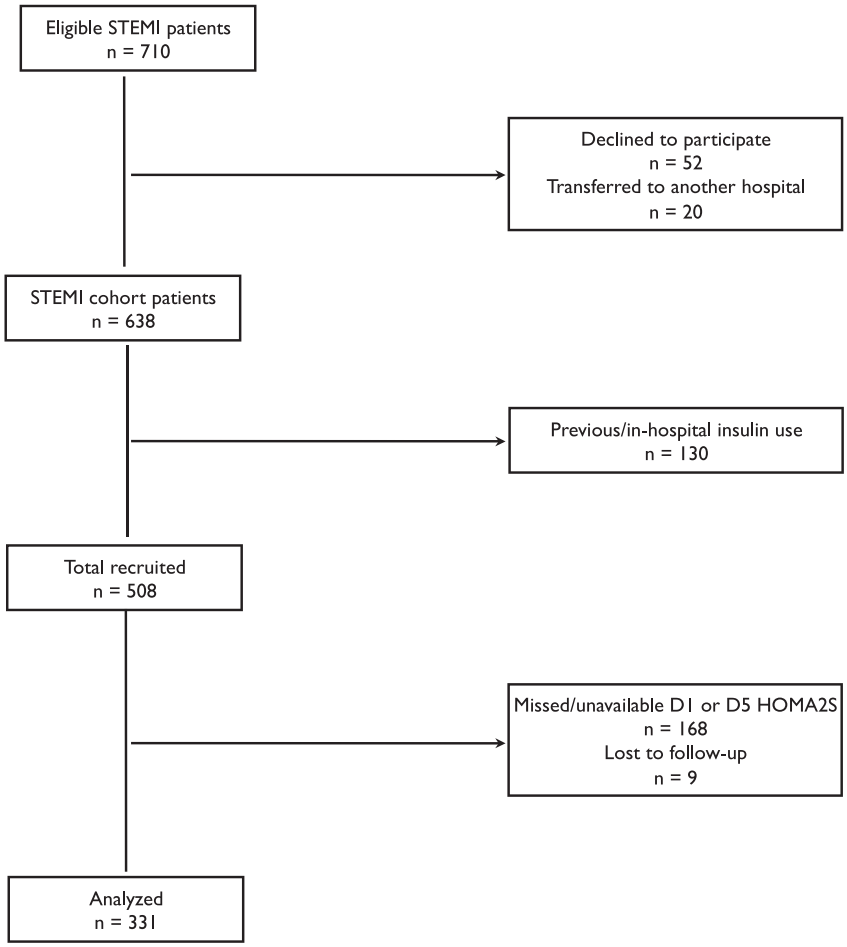

Fig. 1. Flow chart of study patients.

Please cite this article as: F.A. Moura, et al., Adverse outcome has a U-shaped relation with acute phase change in insulin sensitivity after ST-Elevation Myocardial Infarction, Int J Cardiol (2017), https://doi.org/10.1016/j.ijcard.2017.11.111