High plasma HDL-C attenuates stress hyperglycemia during acute phase of myocardial infarction

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ABSTRACT

Objective: During myocardial infarction (MI), a transient decrease of both insulin sensitivity and secretion triggers stress hyperglycemia, which is followed by a substantial increase in mortality. Recent findings in cellular models indicate that HDL may act on glucose homeostasis by improving insulin sensitivity and secretion. In this study, we explored this potential effect in patients during the acute phase of MI.
Methods: Plasma glucose, insulin and C-peptide were measured at admission in the first 24 h and on the fifth day after MI with ST-segment elevation in 183 consecutive non-diabetic patients. Patients were divided into HDL-C quartiles for the analyses (Q1: <31, Q2: 31–38, Q3: 38–47 and Q4: >47 mg/dL). The Homeostasis Model Assessment version 2 was used to assess insulin sensitivity (HOMA2S) and beta-cell function (HOMA2B).
Results: On admission, no difference was found between the quartiles in glucose ($p = 0.6$), insulin ($p = 0.6$) or C-peptide ($p = 0.5$) levels, HOMA2S ($p = 0.9$) or HOMA2B ($p = 1.0$). On the fifth day there was a reduction in glucose levels whose intensity was directly proportional to the HDL-C quartile ($p < 0.001$). At the same time, there was a reduction in plasma insulin ($p < 0.001$) and C-peptides ($p < 0.001$) whose magnitude was inversely proportional to the HDL-C quartile. Consistently, the increase of HOMA2S ($p < 0.001$) and HOMA2B ($p = 0.01$) were also positively associated with HDL-C levels. Furthermore, plasma HDL-C levels were inversely and independently associated with blood glucose change during the acute phase.
Conclusion: This study demonstrates the association between low plasma HDL-C levels and increased duration of stress hyperglycemia during MI and suggests in humans the interaction between HDL and insulin secretion and sensitivity.

1. Introduction

Stress hyperglycemia during myocardial infarction (MI) has been consistently shown to be a strong predictor of mortality in the short and long term, particularly in non-diabetic patients [1]. As the treatment of hyperglycemia reduces mortality in these MI patients, a causal link has been inferred between these two variables [2]. From a mechanistic point of view, the presentation of hyperglycemia during stress is determined by the imbalance between the increase in hepatic production of glucose, the decrease in insulin sensitivity and the capacity of compensating both by enhancing insulin secretion [3]. Factors that act in any of these steps are therefore candidates for triggering or intensifying stress hyperglycemia.

It is well established that during the acute phase of MI, counter-regulatory factors such as cortisol, catecholamines, and cytokines are released in response to the stress and favor hepatic glucose overproduction and peripheral insulin resistance (see Ref. [3] for more details). However, the wide range of variation in the magnitude of stress hyperglycemia during MI and the poor correlation between hyperglycemia and the change in the secretion of these counter-regulatory factors, suggest that other modulatory pathways are also involved [4,5].

In this context, besides the well-established role of high-density lipoprotein (HDL) in reverse cholesterol transport and modulation of inflammation, recent findings indicate a new potential metabolic role for HDL as a player in the modulation of plasma glucose homeostasis. In cell models, it was demonstrated that HDL increases peripheral glucose uptake through activation of AMP-activated

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protein kinase (AMPK) in muscle cells [6,7] and insulin secretion by pancreatic β-cells [8–10]. Data in humans are still unavailable. However, hypothetically, it is plausible that the plasma concentration of HDL may be among the factors that modulate the duration and intensity of stress hyperglycemia. Hence, the present study was designed to explore the association between plasma levels of HDL-C and changes in blood glucose and insulin sensitivity and secretion, in non-diabetic patients, during the acute phase of MI.

2. Methods

2.1. Patients

Consecutive non-diabetic subjects ($n = 183$) who were enrolled into the ongoing Brasilia Heart Study [11] were selected for the study. Briefly, this is a prospective cohort with consecutive patients admitted with ST-segment elevation MI (STEMI). Inclusion criteria are 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, and (iii) myocardial necrosis, as evidenced by increased Creatine Kinase-MB (CK-MB) and troponin levels. The study was approved by the Institutional Ethics Committee, and all patients signed an informed consent.

2.2. Clinical evaluation

Medical evaluation and blood sampling were performed upon admission at the emergency department. A standardized interview was performed to assess medical history, all medications currently used, and lifestyle factors. Hypertension was defined as a repeatedly elevated blood pressure exceeding 140 over 90 mmHg during hospitalization or regular treatment for hypertension prior to the MI. Sedentary lifestyle was defined as <30 min/day of sports activities. Smoking was defined as using 1 or more cigarette/day for more than 1 year before the coronary event. The time of last meal was recorded and the fasting time was calculated based on the interval between the last meal and blood collection.

2.3. Biochemical analyses

The first blood sample was drawn at admission in the emergency department within 24 h after onset of MI symptoms and with a mean fasting time of 474 ± 251 min. The fasting time was equivalent between the 4 quartiles of HDL-C ($p = 0.8$). The second sample was collected after 12-h overnight fasting on the fifth day of hospitalization. The following blood or plasma 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), HDL cholesterol (HDL-C) (HDL cholesterol without sample pretreatment, Roche Diagnostics, Mannheim, Germany), CRP (high-sensitivity CRP, Cardiophase, Dade Behring, Marburg, Germany), insulin (Roche Diagnostics, Mannheim, USA), C-peptide (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA, USA) and HbA1c (Variant II, Bio-Rad Laboratories, Hercules, CA, USA). LDL cholesterol was calculated by the Friedewald formula.

2.4. Glucose homeostasis model assessment

The Homeostasis Model Assessment (HOMA) Calculator version 2.2.2 was used to estimate β cell function (HOMA2B) and insulin sensitivity (HOMA2S) [12]. HOMA2S was based on plasma insulin and HOMA2B on plasma C-peptide. In 2955 non-diabetic subjects (1498 men; 1457 women) aged between 20 and 90 years from The National Health and Examination Nutrition Survey (NHANES), the mean HOMA2B and HOM2S were 93.8 ± 34 and 103.5 ± 48, respectively [13].

Insulin secretion and sensitivity are connected via a negative feedback loop, where pancreatic β-cells compensate for changes in whole body insulin sensitivity by a proportional and reciprocal change in insulin secretion in a rectangular hyperbolic function (i.e. $y = \text{constant}/x$) [14]. Thus, the product of HOMA2B and HOMA2S, i.e. the disposition index (DI), remains approximately constant if only one of these parameters is changed. However, this association is changed when both parameters are simultaneously changed, such as when insulin secretion is not sufficient to accomplish insulin resistance compensation. In order to investigate the existence of changes in HOMA2B, which may occur independently from the HOMA2S variation, we evaluated the DI change across HDL-C quartiles.

2.5. Euglycemic–hyperinsulinemic clamp

In order to validate the HOMA2S index during MI stress condition, euglycemic–hyperinsulinemic clamps were performed on the first and fifth day after MI in a subset of the enrolled patients ($n = 26$). Briefly, at 7:00 A.M. on the day of study, an intravenous cannula was inserted into an antecubital vein, which was kept open with a slow saline drip, and the arm was heated to 50 °C to arterialize the blood. A second cannula was inserted into a contra lateral antecubital vein for infusion of insulin and glucose. After an equilibration period of 30 min, basal samples were collected for determination of plasma glucose and insulin concentrations. After that, euglycemic–hyperinsulinemic clamps were performed by infusing insulin (Novolin R; Novo-Nordisk, Bagsvaerd, Denmark) for 180 min at a rate of 7 pmol kg^{-1} min^{-1}. Euglycemia ($\sim$100 mg/dL) was maintained with a variable-rate infusion of 50% glucose. Blood glucose levels were determined at 10-min intervals, and glucose infusion rates (GIRs) were adjusted as needed. Insulin sensitivity index (Si) was defined as the increase in fractional glucose disappearance per unit increase in plasma insulin, i.e. insulin action (independent of both glucose and insulin levels) [15].

2.6. Statistical methods

Enrolled non-diabetic patients were subdivided into four groups according the quartiles of HDL-C: HDL-Q1 (<31 mg/dL, $n = 49$) HDL-Q2 (31–38 mg/dL, $n = 46$), HDL-Q3 (38–47 mg/dL, $n = 43$) and HDL-Q4 (>47 mg/dL, $n = 45$). Analysis of covariance (ANCOVA) was used to assess the effect of HDL quartiles on insulin, C-peptide, HOMA2 models and DI. Assumptions of the ANCOVA models (linearity, normality of distribution and equal variance) were checked using histograms, normal probability plots and residual scatter plots. Adjustment for baseline levels, age and sex were performed for comparison of mean change of blood glucose, insulin, C-peptide, HOMA2 and DI across HDL quartiles. Multivariate analyses by a binary (dichotomous) logistic regression were performed to verify the independence of the association between HDL-C and the change of blood glucose or DI from admission to the fifth day after MI. Data are presented as mean ± standard deviation for normally distributed data. A two-sided p-value of 0.05 was considered statistically significant. Statistical analyses were performed using SPSS for Windows version 15.0. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.