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# 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 $474 \pm 251$ 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 $93.8 \pm 34$ and $103.5 \pm 48$, 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 (~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.

**Table 1**
Clinical characteristics of enrolled patients.

| | HDL-Q1 | HDL-Q2 | HDL-Q3 | HDL-Q4 | *p* |
|---|---|---|---|---|---|
| *n* | 49 | 46 | 43 | 45 | |
| Age (years) | 59 ± 10 | 60 ± 11 | 64 ± 13 | 64 ± 12 | 0.1 |
| Male (%) | 86 | 87 | 89 | 87 | 0.9 |
| BMI (kg/m$^2$) | 27.9 ± 5.0 | 27.3 ± 4.3 | 26.1 ± 4.8 | 26.5 ± 4.2 | 0.3 |
| Waist circumference (cm) | 99 ± 13 | 98 ± 11 | 92 ± 10 | 90 ± 10 | 0.2 |
| HbA1c (%) | 5.9 ± 0.4 | 5.9 ± 0.4 | 5.9 ± 0.4 | 5.9 ± 0.4 | 0.9 |
| Sedentarity (%) | 51 | 48 | 49 | 53 | 0.9 |
| Smoking habit (%) | 36 | 35 | 39 | 39 | 0.4 |
| Peak of CKMB (u/L) | 231 ± 202 | 245 ± 269 | 258 ± 235 | 212 ± 206 | 0.1 |
| Simvastatin use (%) | 76 | 77 | 77 | 79 | 0.7 |
| Simvastatin dose (mg/day) | 28 ± 23 | 26 ± 25 | 28 ± 24 | 25 ± 24 | 0.7 |
| Beta-blocker use (%) | 70 | 66 | 63 | 62 | 0.7 |

HDL-Q1 = HDL-C < 31 mg/dL; HDL-Q2 = HDL-C 31–38 mg/dL; HDL-Q3 = HDL-C 38–47 mg/dL; and HDL-Q4 = HDL-C > 47 mg/dL; BMI: body mass index; HbA1c: glycosilated hemoglobin; CKMB: creatine kinase-MB.

## 3. Results

### 3.1. Clinical characteristics and change in plasma lipids

Treatment for STEMI was performed in accordance with current guidelines. All patients were treated with tenecteplase, enoxaparin, aspirin, beta blockers, nitrates and, when indicated, inhibitors of angiotensin-converting enzyme. As shown in Table 1, no significant difference was found in clinical characteristics between the participants classified by quartiles of HDL-C. Table 2 presents the laboratory data on admission and on the fifth day of hospitalization. Individuals with higher baseline levels of HDL-C had a greater reduction in these levels in the first 5 days after MI (0 ± 5 vs. −4 ± 6 vs. −5 ± 5 vs. −11 ± 7 mg/dL; $p < 0.001$; first to the last quartile, respectively). Similarly, individuals with higher baseline triglyceride levels had a greater reduction in these levels (−15 ± 95 vs. −14 ± 96 vs. 15 ± 47 vs. 19 ± 51 mg/dL; $p = 0.048$; first to the last quartile of HDL-C, respectively). There was also a significant reduction of LDL-C (−26 ± 35, $p < 0.001$) but it was equivalent in all HDL-C quartiles ($p = 0.2$).

### 3.2. Validation of HOMA2S index during MI

Correlations between SI and HOMA2S measurements were made using absolute values (Fig. 1). As depicted in Fig. 1A, there was a significant and positive correlation between these two methods, which were similar in the assessments made on the first ($r = 0.58$; $p = 0.04$) and on the fifth day after MI ($r = 0.54$; $p = 0.03$). Bland–Altman plots were constructed to identify systematic variation in the assessment of insulin sensitivity by the two methods. Plots of the difference between SI and HOMA2S values versus mean values of both variables (difference plots) demonstrated consistency of the agreement between the two methods in the range of values found in this study (Fig. 1B).

### 3.3. Change in plasma glucose homeostasis

As shown in Table 2, there was no significant difference between groups in the mean plasma glucose, insulin and C-peptide levels at admission. Accordingly, baseline HOMA2B and HOMA2S were also equivalent among the quartiles. On the 5th day after MI, plasma glucose levels fell slightly in patients with low HDL-C and more intensely in those with higher levels of HDL-C ($p < 0.001$ between the quartiles). Likewise, there was a significant reduction in insulin ($p = 0.002$ between the quartiles) and C-peptide levels ($p < 0.001$ between the quartiles), which was more accentuated in patients with higher baseline levels of HDL-C.

On the fifth day after MI, the median values of HOMA2S and HOMA2B increased in all groups, but individuals with higher levels of HDL-C reached higher values (Table 2, $p < 0.001$). As shown in Table 2, DI was equivalent across HDL-C quartiles at baseline,

**Table 2**
Laboratorial data in the first 24 h after MI symptoms onset (admission) and on the 5th day of hospitalization.

| | HDL-Q1 | HDL-Q2 | HDL-Q3 | HDL-Q4 | *p* |
|---|---|---|---|---|---|
| LDL-C at admission (mg/dL) | 122 ± 40 | 127 ± 45 | 126 ± 44 | 129 ± 48 | 0.3 |
| LDL-C on the 5th day (mg/dL) | 95 ± 37 | 97 ± 31 | 95 ± 32 | 102 ± 47 | 0.8 |
| HDL-C at admission (mg/dL) | 27 ± 4 | 35 ± 2 | 43 ± 3 | 55 ± 7 | <0.001 |
| HDL on the 5th day (mg/dL) | 27 ± 8 | 31 ± 7 | 38 ± 8 | 44 ± 9 | <0.001 |
| Triglycerides at admission (mg/dL) | 202 ± 157 | 180 ± 135 | 117 ± 44 | 104 ± 63 | <0.001 |
| Triglycerides on the 5th day (mg/dL) | 187 ± 119 | 164 ± 69 | 132 ± 67 | 123 ± 49 | <0.001 |
| Glucose at admission (mg/dL) | 123 ± 32 | 121 ± 38 | 128 ± 29 | 121 ± 22 | 0.6 |
| Glucose on the 5th day (mg/dL) | 118 ± 30 | 108 ± 31 | 108 ± 27 | 107 ± 20 | 0.01 |
| Insulin at admission | 20 (11–38) | 23 (11–32) | 21 (10–35) | 24 (11–38) | 0.6 |
| Insulin on the 5th day | 12 (7–22) | 15 (8–20) | 9 (6–16) | 6 (5–9) | 0.002 |
| C-peptide at admission (mg/dL) | 4 (3–9) | 4 (3–7) | 4 (3–7) | 4 (3–7) | 0.5 |
| C-peptide on the 5th day (mg/dL) | 4 (3–7) | 4 (3–6) | 3 (2–5) | 2 (1–4) | <0.001 |
| HOMA2S at admission (%) | 29 (14, 51) | 27 (18, 48) | 30 (18, 50) | 32 (19, 53) | 0.9 |
| HOMA2S on the 5th day (%) | 32 (19, 47) | 34 (22, 49) | 41 (29, 59) | 48 (21, 66) | <0.001 |
| HOMA2B at admission (%) | 147 (114, 215) | 154 (122, 197) | 160 (125, 193) | 151 (119, 177) | 1.0 |
| HOMA2B on the 5th day (%) | 157 (109, 210) | 160 (134, 198) | 172 (138, 225) | 173 (132, 212) | 0.03 |
| DI at admission | 4211 (2595, 6372) | 4387 (3201, 6177) | 4466 (3000, 6678) | 5355 (3665, 6761) | 0.5 |
| DI at the 5th day | 4500 (3285, 6167) | 5863 (3623, 7615) | 7373 (5332, 9399) | 7852 (4891, 9970) | 0.003 |

HDL-Q1 = HDL-C < 31 mg/dL; HDL-Q2 = HDL-C 31–38 mg/dL; HDL-Q3 = HDL-C 38–47 mg/dL; and HDL-Q4 = HDL-C > 47 mg/dL; HOMA2S: homeostasis modeling assessment 2 for insulin sensitivity; HOMA2B: homeostasis modeling assessment 2 for insulin secretion; DI: disposition index.

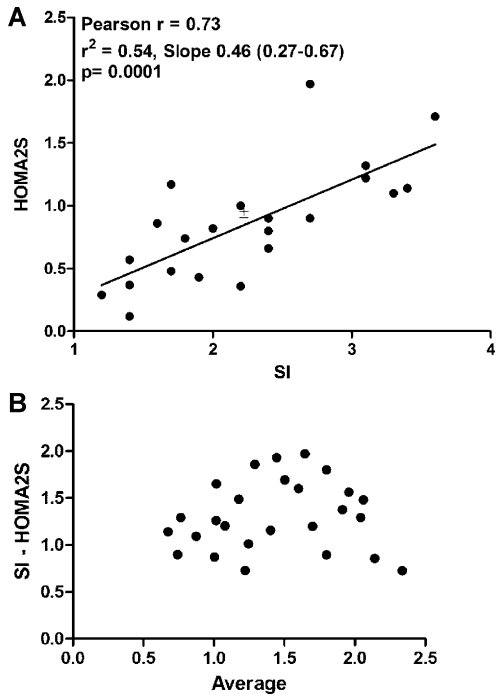


**Fig. 1.** Correlations between insulin sensitivity responses measured by SI and HOMA2S expressed as absolute values (A). (B) The Bland–Altman difference plot of SI versus HOMA2S.

but it was significantly different on the 5th day after MI ($p = 0.003$ between quartiles).

In order to verify the impact of HDL-C variation in modulating insulin secretion and sensitivity, we divided the HDL-C change between the first and fifth day in quartiles (Q1: −36 to −8.9 mg/dL, Q2: −9 to −3.9 mg/dL, Q3: −4 to 0 mg/dL, and Q4: >0 mg/dL). There was no significant association between HDL-C change and the change in insulin secretion or sensitivity during the first five days after MI onset.

### 3.4. Multivariate analyses

A multivariate analysis was performed to investigate the role of known modulators of insulin sensitivity that are often present in individuals with low levels of HDL-C, and whose action can indirectly generate the association observed between stress hyperglycemia and the levels of HDL-C. We considered as potential confounding factors the independent variables: gender, age, sedentarity, HDL-C, triglycerides, waist circumference, CRP levels above the 75th percentile, and the presence of hypertension. Since a strong collinearity exists between HOMA2S and HOMA2B, their combination expressed by DI was selected as the dependent variable for the first model. The change in DI (delta DI) from admission to the fifth day after MI above or below the median value (38.3%) was considered as a qualitative binary variable (Model 1). As shown in Tables 3 and 4, after logistic regression analysis, HDL-C was positively and independently associated with a higher delta DI. In a second model, delta DI was replaced by the presence of a reduction in blood glucose greater than −15 mg/dL from admission to the fifth day (delta glucose). Plasma HDL-C levels were inversely and independently associated with delta glucose (Table 3).

## 4. Discussion

The present study demonstrates that stress hyperglycemia during the acute phase of MI is attenuated in patients with high plasma HDL-C. In addition, the study reveals that greater increases in both insulin sensitivity and the compensatory increase in insulin secretion underlie the drop in blood glucose in these patients.

The hyperinsulinemic–euglycemic clamp is largely considered the gold standard for assessing insulin sensitivity. The suppression of hepatic glucose secretion by constant infusion of insulin makes it possible to estimate the proportion of glucose and insulin needed to keep glucose levels constant and thus estimate insulin sensitivity. However, in studies with large sample sizes, the use of clamps is not feasible because it is expensive, time consuming, and labor intensive. As an alternative, simplified tests such as the HOMA2S index have been used in these larger studies and have been validated by the hyperinsulinemic–euglycemic clamp in individuals in stable clinical conditions [16]. For this study, a new revalidation of HOMA2S was required because the target sample was constituted of individuals under metabolic stress typical of the acute phase of MI. Despite the stressful condition, we found a strong correlation between HOMA2S and SI, which was consistent in both periods of time, admission and fifth day, and over the range of values found in the study.

As MI develops, plasma concentrations of norepinephrine, cortisol, glucagon, and cytokines increase within minutes and start to reduce after the first day depending on the severity of the stress response [3,17]. As commented above, the release of these counter-regulatory factors leads to increased liver glycogenolysis, and decreased insulin sensitivity. Accordingly, the median insulin sensitivity in the first 24 h of MI, as estimated by HOMA2S, was about 30%, a value well below that observed in the general population of nondiabetic individuals (around 100%) [13]. Also, insulin sensitivity consistently improved on the fifth day after MI.

As mentioned above and in contrast to what was expected, i.e. a reciprocal interaction between insulin sensitivity and secretion [14], both HOMA2S, HOMA2B and, consequently, DI indexes increased from admission to the fifth day, suggesting that both insulin sensitivity and secretion were improved. Such improvement was more accentuated among individuals with higher HDL-C concentrations. In fact, recent studies in cell models suggest that HDL particles can influence blood glucose homeostasis via multiple actions both dependent and independent of insulin secretion.

**Table 3**
Binary logistic regression considering delta DI > 38.3% (Model 1) as dependent variable.

| Model 1 | *B* | S.E. | Wald | *p* | Exp(*B*) | 95% C.I. for Exp(*B*) | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| Gender (male) | 0.088 | 0.416 | 0.044 | 0.833 | 1.092 | 0.483 | 2.469 |
| Age (years) | −0.033 | 0.018 | 3.194 | 0.074 | 0.968 | 0.934 | 1.003 |
| Sedentarity | −0.089 | 0.369 | 0.059 | 0.809 | 0.915 | 0.444 | 1.884 |
| Waist circumference (cm) | 0.031 | 0.017 | 3.125 | 0.077 | 1.031 | 0.997 | 1.067 |
| Triglycerides (mg/dL) | −0.003 | 0.002 | 1.518 | 0.218 | 0.997 | 0.993 | 1.002 |
| Hypertension | −0.630 | 0.399 | 2.490 | 0.115 | 0.533 | 0.244 | 1.165 |
| HDL-C (mg/dL) | 0.068 | 0.020 | 12.303 | 0.0001 | 1.071 | 1.031 | 1.113 |
| CRP > 75th percentile | 0.280 | 0.419 | 0.448 | 0.503 | 1.324 | 0.582 | 3.008 |
| Constant | −3.234 | 2.237 | 2.090 | 0.148 | 0.039 | | |

**Table 4**
Binary logistic regression considering delta blood glucose < −15 mg/dL (Model 2) as dependent variable.

| Model 2 | *B* | S.E. | Wald | *p* | Exp(*B*) | 95% C.I. for Exp(*B*) | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| Gender (male) | 0.573 | 0.560 | 1.050 | 0.306 | 1.774 | 0.592 | 5.314 |
| Age (years) | −0.002 | 0.024 | 0.004 | 0.949 | 0.998 | 0.954 | 1.046 |
| Sedentarity | −0.109 | 0.519 | 0.045 | 0.833 | 0.896 | 0.324 | 2.478 |
| Waist circumference (cm) | 0.010 | 0.025 | 0.150 | 0.698 | 1.010 | 0.961 | 1.061 |
| Triglycerides (mg/dL) | 0.002 | 0.002 | 0.484 | 0.487 | 1.002 | 0.997 | 1.006 |
| Hypertension | 0.503 | 0.553 | 0.826 | 0.363 | 1.654 | 0.559 | 4.891 |
| HDL-C (mg/dL) | 0.062 | 0.028 | 4.875 | 0.027 | 1.064 | 1.007 | 1.124 |
| CRP > 75th percentile | 0.596 | 0.574 | 1.077 | 0.299 | 1.815 | 0.589 | 5.596 |
| Constant | −3.791 | 3.427 | 1.223 | 0.269 | 0.023 | | |

In skeletal muscle cells, apolipoprotein (Apo) A-I, a major protein constituent of HDL, induces phosphorylation of AMPK and acetyl-coenzyme A carboxylase (ACC), thus increasing glucose uptake and endocytosis [17]. In addition, HDL may also increase insulin secretion in pancreatic β-cells via direct action by activating the ATP-binding cassette transporter A1 (ABCA1) [9] and via indirect action by inhibiting the activation of the c-Jun $NH_2$-terminal kinase (JNK) pathway induced by oxidized LDL [8]. Fryirs et al., [10] recently found that both Apo A-I and Apo A-II increase the production and secretion of insulin through a mechanism equally dependent on ABCA1 and scavenger receptor B1 (SR-B1) transporters in pancreatic β-cells.

The increase in cholesterol efflux induced by the apolipoproteins A-I and A-II is appointed as the likely causal mechanism. Delipidation of cholesterol-enriched cells may facilitate the docking and fusion of insulin-containing granules from the readily releasable pool and thus lead to an increase of insulin secretion [9,10]. In subjects with type 2 diabetes mellitus, intravenous infusion of reconstituted HDL particles sharply reduces plasma glucose and increases plasma insulin as compared to administration of a placebo [6]. In these individuals, skeletal muscle biopsies demonstrate increased ACC phosphorylation.

Indirectly, high plasma levels of HDL can attenuate the induction of insulin resistance through its anti-inflammatory effects. Indeed, *in vitro* studies demonstrate a role of HDL as a buffer mechanism for oxidative stress and inflammation [18]. To date, however, little is known about the interaction between HDL particles and the inflammatory response during the acute phase of acute coronary events.

Despite the mechanistic evidence above, it is reasonable to question whether these effects result from the direct action of HDL or are induced by metabolic and clinical factors commonly found in subjects with low HDL plasma levels. For example, plasma HDL is reduced by age, male gender, increased body weight, hypertriglyceridemia, hypertension and inflammatory states. All these characteristics may influence glucose homeostasis. To clarify this issue, multivariate logistic regression analyses were performed using the change of DI or of blood glucose between admission and the fifth day as dependent variables. In both models, HDL-C plasma concentration was independently associated with the improvement of the acute imbalance of glucose homeostasis.

It is noteworthy to mention that the change in HDL-C during the first five days of hospitalization was not associated with the change in blood glucose, insulin sensitivity or secretion. Yet, although studies are needed to clarify this finding, it can be inferred from this study that simply increasing or decreasing the HDL concentrations during the acute phase of MI does not guarantee the modulation of its interaction on glucose homeostasis.

Some limitations should be considered when interpreting the findings of this study. Despite carrying out multivariate analysis, the study is not able to detect the role of unmeasured or unknown factors as potential links between HDL levels and glucose homeostasis. We defined as the main exclusion criterion the presence of diabetes mellitus identified by a previous diagnosis or, in its absence, by the presence of HbA1c levels greater than 6.5%, consistently with the report of the World Health Organization [19]. As the elevation of blood glucose typically occurs in the acute phase of MI, we could not use blood glucose to improve the exclusion criterion. However, we repeated the analysis considering only patients admitted with HbA1c < 6.0% ($n = 123$) and we found the same results. Although there is substantial pathophysiological mechanisms underlying the association between HDL-C levels and the change in insulin sensitivity during MI, it is possible that individuals who do not yet have glucose intolerance at normal conditions but who have reduced tolerance to prolonged hyperglycemic stress manifest low HDL-C as part of their clinical phenotype. This study is not able to exclude this possibility. Finally, as the study was conducted in subjects with STEMI, the present findings should not be extrapolated to other populations. Nevertheless, these findings can indeed open the door to debate on how to use the HDL-C concentrations in plasma, either as a marker or therapeutic target, in the setting of stress hyperglycemia.

In conclusion, this study provided the first evidence in humans suggesting that low HDL-C is associated with a delayed recovery of stress hyperglycemia, and reduced insulin secretion and sensitivity induced during acute phase of MI. Taking into consideration the robust association between hyperglycemia and adverse clinical outcome after MI, this association between HDL-C and glucose homeostasis under acute stress deserves attention and further exploration.

## Disclosures

The authors state that they have no conflict of interest.

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