# Early Glucometabolic Profile in Patients with Acute Coronary Syndromes and Metabolic Syndrome

*Carlos M C Monteiro, Luciene Oliveira, Maria C O Izar, Tatiana Helfenstein, Andreza O Santos, Simone M Fischer, Sahana W Barros, Luiz F M Pinheiro, Antonio C C Carvalho, Francisco A H Fonseca*

*Universidade Federal de São Paulo, São Paulo, SP - Brazil*

## Summary

**Background: Patients with metabolic syndrome (MetS) are at high coronary risk and beta-cell dysfunction or insulin resistance might predict an additional risk for early cardiovascular events.**

**Objective: This study aimed to evaluate early glucometabolic alterations in patients with MetS, but without previously known type 2 diabetes, after acute coronary syndrome.**

**Methods: A total of 114 patients were submitted to an oral glucose tolerance test (OGTT) 1-3 days after hospital discharge due to myocardial infarction or unstable angina. Based on the OGTT, we defined three groups of patients: normal glucose tolerance (NGT; n=26), impaired glucose tolerance (IGT; n=39), or diabetes (DM; n=49). The homeostasis model assessment (HOMA-IR) was used to measure insulin resistance; beta-cell responsiveness was assessed by the insulinogenic index at 30 min (ΔI30/ΔG30).**

**Results: Based on the HOMA-IR, patients with DM were more insulin-resistant than those with NGT or IGT (p<0.001). According to the insulinogenic index, the beta-cell responsiveness was also impaired in subjects with DM (p<0.001 *vs* NGT or IGT).**

**Conclusion: High rates of glucometabolic alterations were found after acute coronary syndrome in patients with MetS. As these abnormalities markedly increase the risk for adverse outcomes, early OGTT among MetS patients might be used to identify those at the highest coronary risk. (Arq Bras Cardiol 2009;92(2):89-93)**

**Key words: Insulin resistance; metabolic syndrome; acute coronary syndrome; diabetes mellitus, type 2; insulin-secreting cells.**

## Introduction

Recently, closer associations between glucometabolic alterations and coronary artery disease have been established[1,2]. Glucose abnormalities, observed during the acute phase of coronary syndromes (ACS), increase the risk of adverse outcomes[3,4]. In addition, those patients with known diabetes mellitus and previous myocardial infarction present the highest risk for cardiovascular mortality[5].

Several studies have recognized metabolic syndrome (MetS) as an additional risk factor for cardiovascular events, especially among patients with known diabetes mellitus[6-8]. All these aspects suggest the need of early identification of patients with occult diabetes or presenting glucometabolic abnormalities. In fact, for these patients, a more aggressive treatment, including lifestyle changes, and early achievement of lipid and blood pressure goals could contribute to better outcomes[9,10].

Therefore, the aim of this study is to compare the glucometabolic profile, based on the early responses to OGTT, in patients with MetS and recent ACS.

## Methods

Patients selected from the Federal University of Sao Paulo were included in the present study if they met the following inclusion criteria: recent admission due to ACS (acute myocardial infarction or unstable angina pectoris), no previously known diabetes mellitus, age 30-75 years, MetS according to the revised National Cholesterol Education Program/Adult Treatment Panel (NCEP/ATP III)[11], and stable hemodynamic conditions in the first 1-3 days after hospital discharge. Patients were excluded if they had used hypolipidemic drugs in the last 30 days or presented LDL-C ≥ 130 mg/dL at hospital admission. A total of 114 participants of both sexes were enrolled and the. Informed consent was obtained from all patients. This study was approved by the local ethics committee.

**Mailing address: Francisco Antônio Helfenstein Fonseca •**
Rua Pedro de Toledo, 276 - V. Clementino - 04039-001 - São Paulo, SP - Brazil
E-mail: fahfonseca@terra.com.br, ffonseca@cardiol.br
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Fasting plasma lipids (cholesterol, HDL-C, triglycerides) were measured using a standardized kit; LDL-C was estimated by the formula of Friedewald, and apolipoproteins A1 and B were determined by nephelometry. The Oral glucose tolerance test (OGTT, 75 g glucose in 200 ml water) was performed 1-3 days after hospital discharge, after three days of nutrition counseling, based on the NCEP/ATP III guidelines and for appropriate and non-restrictive intake of carbohydrates. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as insulin (mU/L) X (glucose [mg/dL] X 0.055)/22.5[12]. For this calculation, we used the mean of three consecutive samples of fasting insulin. The insulinogenic index was calculated as the difference between the 30 min and 0 min OGTT plasma insulin values divided by the difference between the corresponding plasma glucose values (ΔI30/ΔG30). The area under the curve (AUC) for glucose and insulin were determined based on the blood samples obtained before (t=0) and 30, 60, 90, and 120 min after oral glucose load. Adiponectin was measured by enzyme-linked immunosorbent assay (ELISA) using a commercial kit (Human Adiponectin/Acrp30 Immunoassay - Quantiquine, R&D Systems). Glycated hemoglobin (HbA1c) was measured using high-performance liquid chromatography.

The severity of coronary atherosclerosis was evaluated through the Gensini score, which depends on the degree of luminal narrowing and importance of the coronary stenosis site[13]. The score evaluates the severity and effects of multiple obstructions, quality of the coronary arteries and the influence of collateral vessels.

To determine differences between the three groups formed after OGTT (NGT, IGT and DM), continuous variables were compared by ANOVA. When necessary, values were log-transformed. Categorical variables were compared using chi-square tests. All tests were 2-tailed, and a p value $< 0.05$ defined statistical significance. All analyses were performed with SPSS 11.5 for Windows (SPSS Inc, Chicago, IL).

## Results

Major characteristics of the study population are shown in Table 1. One to three days after hospital discharge, only 23% (n=26) of the patients had NGT, while 34% (n=39) had IGT and 43% (n=49) were classified as having DM. In-hospital medical treatment and procedures were similar among the groups. Subjects with NGT, IGT and DM were also comparable regarding age and sex distribution, but higher BMI was observed in DM subjects (p=0.036 vs. NGT), with no differences observed regarding waist circumference. The extension and severity of the coronary artery disease, evaluated by the Gensini score, did not differ among the groups. Lipid and apolipoprotein values were similar among the groups. Fasting plasma glucose values were higher in DM patients, as well as 120 minutes after an oral glucose load (p<0.001 *vs* NGT and IGT). Fasting insulin values were also higher in DM subjects (p<0.001 *vs* NGT and p<0.004 *vs* IGT).

Drug therapies at hospital discharge are shown in Table 2. The only difference among the groups was the higher prevalence of hypoglycemic drug use in subjects with DM.

HOMA-IR was higher in DM subjects (p<0.001 *vs* IGT and NGT), as well as the insulinogenic index (p<0.001 *vs* NGT and IGT) [Fig 1]. Plasma adiponectin values did not differ among the groups.

Figure 2 shows the AUC for glucose and insulin. Patients with DM presented higher glucose $_{AUC}$ (p<0.001 *vs* NGT and IGT). Insulin $_{AUC}$ was also higher in subjects with DM (p<0.017 *vs* NGT, p<0.001 *vs* IGT).

## Discussion

In recent years, MetS has been commonly reported among patients with ACS[6,14]. This study shows, for the first time, the major glucometabolic abnormalities in patients with MetS, but without previously known type 2 diabetes in the acute phase of coronary syndromes.

The OGTT responses performed 1-3 d after hospital discharge disclosed high rates of IGT (34%) and DM (43%). Based on the HOMA-IR, patients with DM were more insulin-resistant than those with NGT or IGT. Furthermore, according to the insulinogenic index (ΔI30/ΔG30), the beta-cell responsiveness was also impaired in subjects with DM, when compared with NGT or IGT patients.

Even considering that ACS is a stressful situation, which can explain the high rate of glucometabolic alterations on MetS subjects, these abnormalities are associated with adverse outcomes. Feinberg et al[5] reported, in 1,060 consecutive patients with no previous diagnosis of diabetes, that MetS is an independent predictor of 30-day and 1-year mortality. However, the authors also observed that among those patients, the ones with fasting glycemia > 140 mg/dL were at the highest mortality risk

In our study, we found that insulin resistance was more frequent in patients with no previous diagnosis of DM. The independent association of insulin resistance with coronary disease is still controversial. Tenenbaum et al[15] evaluated the predictive value of HOMA-IR for new major cardiovascular events in 2,938 subjects with preexisting coronary disease. After multivariate analysis, they concluded that insulin resistance is an independent risk factor for cardiovascular events and new-onset diabetes[15]. In the Multi-Ethnic Study of Atherosclerosis (MESA)[2] subclinical atherosclerosis was assessed in 5,810 participants without diabetes and the HOMA-IR was associated with subclinical atherosclerosis; however, the association was not independent after adjustment for non-glucose MetS components.

The present study also showed that DM subjects presented lower beta-cell responsiveness. We used the insulinogenic index to estimate beta-cell function. In comparative studies to evaluate insulin secretion, this index was considered closely related to insulin secretion[16]. In addition, as part of our DM patients were under use of hypoglycemic drugs at hospital discharge, this method appeared to be more sensitive, considering it measures the early insulin response to oral glucose stimulation.

Both insulin deficiency and insulin resistance can be associated with endothelial dysfunction, as insulin-signaling pathways include the production of nitric oxide (NO) and secretion of endothelin-1. In patients with MetS, inflammatory

**Table 1 – Characteristics of study population and major laboratory findings**

| Variable | NGT n=26 | IGT n=39 | DM n=49 | p |
|---|---|---|---|---|
| Age, years | 54±2 | 57±1 | 58±1 | 0.18 |
| Male/female, % | 77/23 | 67/33 | 55/45 | 0.16 |
| BMI, kg/m$^2$ | 28.4±0.8 | 29.8±0.6 | 31.3±0.8 | 0.04* |
| Waist circumference, cm | 102±2 | 103±2 | 107±2 | 0.10 |
| Fasting glucose, mg/dL | 100±2 | 102±2 | 158±8 | 0.001§ |
| Fasting insulin, pmol/L | 66±6 | 76±6 | 113±10 | 0.001§ |
| HbA1c, % | 5.32±0.11 | 5.65±0.06 | 7.85±0.29 | 0.001§ |
| Glucose AUC, mmol.L$^{-1}$.min$^{-1}$ | 933±24 | 1194±23 | 1880±68 | 0.001§ |
| Insulin AUC, pmol. L$^{-1}$.min$^{-1}$ | 74710±9749 | 83724±7149 | 45803±4838 | 0.001¶ |
| HOMA-IR, mU.mmol$^{-1}$.L$^{-1}$ | 3.04±0.26 | 3.67±0.31 | 8.19±0.80 | 0.001§ |
| ΔI30/ΔG30, pmol/mmol | 187±20 | 120±14 | 37±5 | 0.001¶ |
| Adiponectin, IU/mL | 580±80 | 619±83 | 684±71 | 0.65 |
| Blood creatinine, mg/dL | 1.05±0.05 | 1.09±0.04 | 1.02±0.05 | 0.62 |
| Total cholesterol, mg/dL | 191±8 | 188±6 | 193±5 | 0.85 |
| LDL-C, mg/dL | 118±7 | 115±6 | 110±6 | 0.68 |
| HDL-C, mg/dL | 40±2 | 39±1 | 41±1 | 0.52 |
| Triglycerides, mg/dL | 166±8 | 172±9 | 189±14 | 0.40 |
| Apo A1, g/L | 1.07±0.03 | 1.06±0.02 | 1.08±0.03 | 0.88 |
| Apo B, g/L | 1.19±0.05 | 1.14±0.05 | 1.12±0.04 | 0.59 |
| SBP, mm Hg | 130±4 | 131±4 | 134±4 | 0.82 |
| DBP, mm Hg | 85±3 | 87±3 | 86±2 | 0.89 |
| UA/AMI, % | 58/42 | 49/51 | 53/47 | 0.77 |
| Gensini score | 24.8±4.5 | 19.4±3.4 | 27.9±4.6 | 0.38 |
| Thrombolysis, % | 12 | 6 | 10 | 0.64 |
| PI, % | 42 | 36 | 45 | 0.91 |

*Values are expressed as means±SEM; AUC - area under curve; HOMA-IR - homeostasis model assessment of insulin resistance; ΔI30/ΔG30 - insulinogenic index; UA - unstable angina; AMI - acute myocardial infarction; PI - in-hospital percutaneous intervention; *DM > NGT; § DM > NGT and IGT; DM < NGT and IGT.*

**Table 2 – Current drug therapies**

| | NGT | IGT | DM | P |
|---|---|---|---|---|
| Aspirin, % | 85 | 92 | 96 | 0.64 |
| Clopidogrel, % | 31 | 25 | 41 | 0.40 |
| Beta-blockers, % | 88 | 80 | 90 | 0.70 |
| Metformin, % | 0 | 0 | 24 | 0.001* |
| Sulfonylurea, % | 0 | 0 | 41 | 0.001* |
| Insulin, % | 0 | 0 | 20 | 0.001* |
| ACEI,% | 69 | 78 | 86 | 0.52 |
| CCB, % | 19 | 11 | 24 | 0.36 |

*Current drug therapies at hospital discharge (%); ACEI - angiotensin-converting enzyme inhibitors; CCB - calcium channel blockers; * DM > NGT and IGT.*

stimuli can cause an additional imbalance between NO production and endothelin-1 secretion, leading to reduced blood flow and impaired glucose uptake in peripheral muscle[17]. In addition, endothelial dysfunction has been related to the development of atherosclerosis and cardiovascular events[18,19].

In our study, in-hospital procedures (CABG, percutaneous intervention) and the extension of coronary disease evaluated by the Gensini score were similar among the groups. However, our study was not powered to detect significant differences regarding the burden of atherosclerosis or cardiac events. However, Boulon et al[20], evaluating the impact of MetS in a follow-up of 480 consecutive patients with ACS, reported an increase in total mortality in the MetS group compared with the non-MetS group[20]. In the Women's Ischemia Syndrome Evaluation (WISE) study, coronary angiography was obtained in 755 women due to suspected myocardial ischemia. When

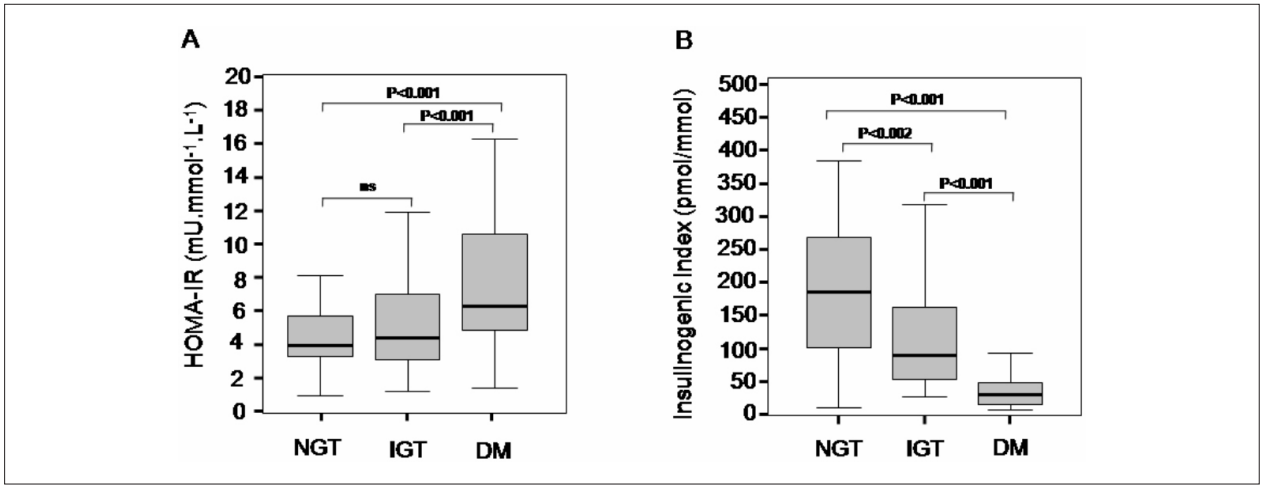


*Figure 1 - A - Box-plots showing the homeostasis model assessment (HOMA-IR) values obtained for subjects with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or diabetes (DM). Based on the HOMA-IR, patients with DM were more insulin-resistant than those with NGT or IGT (p<0.001). B - Box-plots showing the insulinogenic index at 30 min (ΔI30/ΔG30) in NGT, IGT, and DM subjects. B - According to this parameter, the beta-cell responsiveness was also impaired in subjects with DM (p<0.001 vs NGT or IGT), and IGT patients had lower values than NGT subjects (p<0.002).*

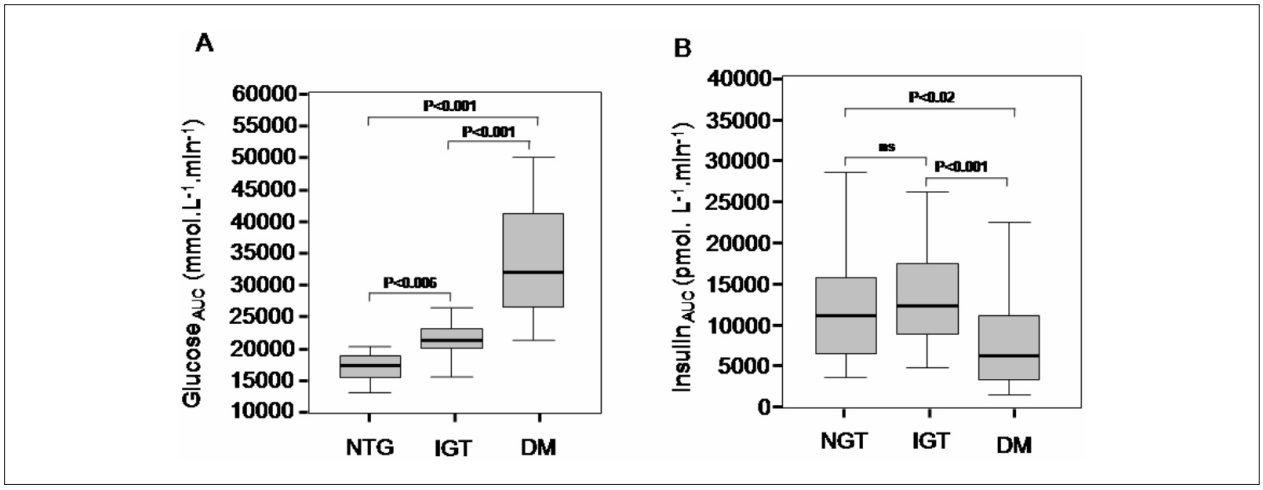


*Figure 2 - A - Box-plots showing the values obtained for the area under the curve for glucose (Glucose AUC). Higher values were observed in DM patients (p<0.001 vs NGT and IGT), and also in IGT when compared with NGT subjects (p<0.006). B - Box-plots showing the values obtained for the area under the curve for insulin (Insulin AUC). Subjects with DM had lower Insulin AUC values (p<0.02 vs NGT; p<0.001 vs IGT).*

compared with women that presented normal metabolic status, those with MetS had a lower 4-year survival and event-free survival rate (death, nonfatal myocardial infarction, stroke, or congestive heart failure), and when stratified by the presence of significant coronary disease at the angiography, women with MetS were also at higher risk of cardiovascular events[21].

Recently, studies aimed to evaluate the long-term prognosis of IGT or newly-diagnosed DM after myocardial infarction have identified these glucometabolic abnormalities after OGTT as the strongest predictors of death and major cardiovascular events[22-24].

In addition, the Euro Heart Survey showed that 20-30% of patients with either acute coronary syndrome or chronic coronary artery disease presented with newly detected glucose intolerance or diabetes and an OGTT was considered the most appropriate method for the clinical assessment of glucometabolic status in these patients[25]. Finally, the Munich Myocardial Infarction Registry showed the relevance of the in-hospital diagnosis of diabetes mellitus, to promote the early establishment of strategies to reduce cardiovascular mortality[26], which is endorsed by both the American College of Cardiology/American Heart Association and American Diabetes Association/American College of Endocrinology for glycemic control in patients with acute coronary syndrome, as a Class IIa recommendation[27].

In conclusion, this study describes high rates of impaired glucose metabolism, including insulin resistance and beta-cell dysfunction, in subjects with MetS at the acute phase of coronary

syndromes. The study reinforces that an early OGTT can identify subjects with DM or IGT, allowing a more appropriate treatment to be established, as well as the achievement of target lipid, blood pressure and glucose metabolism goals, to improve outcomes in this high-risk population.

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### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Study Association

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