Influence of Leukocytes and Glycemia on the Prognosis of Patients with Acute Myocardial Infarction

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Summary

Background: Previous studies have demonstrated that leukocytosis and hyperglycemia verified at the admission of patients with acute myocardial infarction (AMI) are associated with intrahospital mortality. However, little is known on the long-term impact of these markers.

Objective: To evaluate the short-and long-term influence of the levels of glucose and leukocytes on the prognosis of patients with AMI.

Methods: A total of 809 patients with AMI were retrospectively assessed (mean age: 63.2 ± 12.87 yrs) and prospectively and consecutively included in a specific database.

Results: a) At the intrahospital phase, the mean values were compared between patients that died and those who survived: Leukocytosis: 12156±5977 *vs* 10337±3528 (p=0.004, 95%CI = 976-2663); Glucose 176±105 mg/dl *vs* 140±72 mg/dl (p<0.001, 95%CI = 19.4 – 52.6), respectively. b) With the adjusted mode, the same pattern was observed [p values: 0.002 (t-ratio 3.05), 0.04 (t-ratio 2.06), respectively]. c) Long-term follow-up: the univariate analysis showed P values of 0.001 (t-ratio 3.3), <0.001 (t-ratio 4.16), respectively. The multivariate analysis showed P=0.001 (t-ratio 3.35), 0.08 (t-ratio 1.75), respectively. (d) After the exclusion of the intrahospital deaths, the leukocyte (P=0.989) and glucose levels (P=0.144) did not remain significantly correlated with mortality. The same result was observed at the multivariate analysis.

Conclusion: The levels of glucose and leukocytes at the hospital admission of patients with AMI are excellent predictors of intrahospital mortality and poor predictors of long-term death. (Arq Bras Cardiol 2009;92(2):84-88)

Key words: Leukocytosis; glucose; myocardial infarction.

Introduction

Patients with unstable myocardial ischemic syndromes (UMIS) must be routinely submitted to risk stratification when admitted at the hospital. The objective of this early stratification is to determine the risk and prognosis of these patients, which allows establishing a more adequate therapeutic management and clinical follow-up of the patients. In this sense, the classification by Braunwald[A] and the risk scores published by the TIMI group (Thrombolysis In Myocardial Infarction)[B,C], for UMIS without ST-elevation as well as for acute myocardial infarction (AMI) with ST-elevation, have been largely used for early stratification. However, other risk markers have been investigated in an attempt to make the short- and long-term prognostic assessments more accurate. Previous studies demonstrated that leukocytosis and hyperglycemia verified at the hospital admission of patients with AMI are correlated with intrahospital mortality[d-7]. However, little is known about the long-term impact of these markers.

Thus, the main purpose of this study was to evaluate the short- and long-term influence of the levels of glucose and leukocytes on the prognosis of patients with AMI and compare the impact of these "new" markers with that of the "traditional" ones, such as left ventricular (LV) ejection fraction (EF) and age.

Methods

This is a unicentric study, in which all patients were selected from an Intensive Care Coronary Unit. A total of 809 patients with AMI were retrospectively assessed (mean age: 63.2 ± 12.87 yrs) and prospectively and consecutively included in a specific database, between February 1998 and July 2005. The criteria used for the AMI diagnosis were: troponin curve or fraction of creatine kinase (CK-MB) associated to at least of the following: ischemic symptoms, development of pathological Q waves at the electrocardiogram (ECG), electrocardiographic alterations indicative of ischemia (ST elevation or depression) or post-coronary intervention.

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The patients were followed for up to 6.4 years (mean survival time of 5.15 years), with annual prospective assessments in relation to mortality. The follow-up of the study population was carried out annually by phone or personal interview. The patients (or their family members) were contacted by phone, visits to the office or active personal search (personal search at the workplace, residence, neighbors' houses, etc).

The values of the first leukocyte and glycemia measurements were analyzed in relation to the intrahospital and long-term prognosis. The blood collection for glycemia and leukocytosis measurement was carried out at the moment of the hospital admission.

In the adjusted models, the following variables were considered: history of angioplasty, myocardial revascularization surgery, myocardial infarction, diabetes, smoking, history of heart failure (HF), age, sex, heart rate (HR), systolic arterial pressure (SAP), ST-segment elevation, glycemia, leukocytes, EF (first echocardiogram; Simpson's method), presence of fibrinolysis and primary angioplasty.

For the intrahospital phase, the Student's t test or Kruskal-Wallis test (univariate analysis) and logistic regression (multivariate analysis) were used. For the long-term analysis, Cox proportional hazards estimation was used. The stepwise method[8] (with an entry of 0.10 and removal of 0.10), was used for the logistic regression analysis.

Results

A. Study population

The data regarding the studied population are shown in Table 1.

Table 1 - Characteristics of the studied population

Characteristic	Number of Patients (%) Total = 809
Age (yrs)	63.20 ± 12.87
Ejection Fraction	53.90 ± 15%
Previous history	
Angioplasty	99 (12.2)
MRS	115 (14.2)
Diabetes	212 (26.3)
Smoking	240 (29.6)
AMI	211 (26.0)
Heart failure	41 (5.0)
Sex	
Male	593 (73.3)
Female	216 (26.7)
Electrocardiogram	
With ST elevation	487 (60.3)
Without ST elevation	322 (39.7)
Reperfusion	
Fibrinolysis	242 (49.7)*
Primary Angioplasty	144 (29.6)*

*MRS - myocardial revascularization surgery; AMI - acute myocardial infarction. *Percentage of patients with st elevation.*

B. Intra-hospital phase

At the intrahospital phase, 92 patients (11.37%) died. The mean time until death was 94 hours (95%CI; 60.90-127.0). The mean values measured for the variables were compared between patients that died and those who survived: Leukocytosis 12156±5977 *vs* 10337±3528 (p=0.004, 95% CI = 976-2663); Glucose 176±105 mg/dl *vs* 140±72 mg/dl (p<0.001, 95% CI = 19.40-52.60), respectively. As it can be observed, the two analyzed variables significantly correlated with the worst prognosis.

Table 2 demonstrates the results of the multivariate model. After the logistic regression analysis of 16 variables, through the stepwise model (with an entry of 0.10 and removal of 0.10), it was observed that only 5 variables significantly and independently correlated with the intrahospital mortality: glycemia, leukocytes, age, EF and SAP.

Table 2 - Prognostic value of the variables analyzed during the intrahospital phase: multivariate analysis

Variables	t-ratio	P
Leucocytes	3,05	0,002
Glycemia	2,06	0,04
Age	6,07	<0,001
EF (%)	-3,46	0,001
SAP	-5,56	<0,001

EF - ejection fraction; SAP - systolic arterial pressure.

C. Late follow-up

C.1. General population

During the extra-hospital phase, there were 94 additional deaths. The probability of global survival was 77% (Kaplan-Mayer). Regarding the long-term follow-up, considering the totality of patients, significant correlations were observed between glycemia/leukocytes and mortality, as shown in Table 3. Table 4 shows that, in the multivariate model, six analyzed variables remained as prognostic factors for the long-term evolution in the global population. However, glycemia showed only a tendency to correlate with mortality.

Table 3 - Long-term prognostic value of the analyzed variables: univariate analysis for the general population

Variables	t-ratio	P
Leukocytes	3.30	0.001
Glycemia (mg/dl)	4.16	<0.001

C.2. Patients that survived the intrahospital phase

As shown in Table 5, when the intrahospital deaths were excluded, leukocytes and glycemia levels no longer correlated

with the long-term evolution. In other words, the prognostic value of leukocytes and glycemia levels is restricted to the intrahospital phase, presenting no impact after hospital discharge. This behavior does not present alterations in the adjusted models, as shown in Table 6, where only the history of HF, age and EF correlate with mortality.

Discussion

In the last three decades, the treatment of AMI showed significant advancement, which resulted in the decrease of the morbimortality related to the disease[9]. That occurred mainly due to new pharmacological and mechanical primary reperfusion strategies, multiple anti-aggregation, in addition to the broad use of invasive stratification and the possibility of revascularization with angioplasty and stents[10].

However, patients with UMIS have different characteristics, which determine their risk and prognosis variability. Some of these patients benefit from aggressive therapeutic measures, such as percutaneous invasive approach and strict glycemia control[11,12].

In this sense, to identify patients at higher risk has been a constant concern in literature. In addition to the studies to validate risk scores and the variables that are traditionally associated with a poor prognosis, such as age and left ventricular dysfunction, investigators have recently worked on the identification of new prognostic variables, such as inflammatory markers, natriuretic peptide, leukocytosis and hyperglycemia, among others[12-15].

Diabetic patients are recognized as being high-risk patients and having worse short- and long-term prognosis after AMI. The MONICA report showed that the mortality for diabetic and non-diabetic infarcted patients, after 28 days of evolution, was 12.6% and 7.3%, respectively[16]. Therefore, the inclusion of diabetes mellitus in the early risk stratification is justified.

However, the presence of hyperglycemia was also identified as a poor prognosis factor in non-diabetic infarcted patients[17-19]. It was recently demonstrated that hyperglycemia is still a poor prognosis factor also in patients submitted to percutaneous coronary intervention, regardless of the presence of diabetes[20]. It was also verified in this and in other studies[21,22] that there is an association between hyperglycemia, no-reflow phenomena and ventricular remodeling, which are known factors of severity and worse prognosis in the evolution of patients with AMI[23].

Similarly, another study demonstrated that hyperglycemia, but not diabetes, was a poor intrahospital prognostic factor[24]. Regarding the long-term follow-up, previous studies demonstrated that hyperglycemia, regardless of the presence of diabetes, was also a risk factor for mortality in patients with AMI[25-27].

The data obtained in our study were similar to those found by other authors regarding the influence of glycemia on mortality. Glycemia levels at the hospital admission were significantly higher in patients that died during the hospital stay. During the follow-up of more than 6 years, hyperglycemia remained as a bad prognosis factor, although the adjusted model showed only a tendency to worse mortality. However, after the exclusion of the intrahospital deaths, the variables age, ejection fraction (EF) and history of HF remained significantly correlated with mortality, but not the levels of leukocytes or glycemia. This fact might be related to the hypotheses that hyperglycemia is not only a prognostic marker, but a direct cardiovascular system aggressor in the acute phase of AMI.

Experimental studies demonstrated that hyperglycemia is capable of causing platelet thrombosis, increasing the circulation of leukocyte adhesion molecules and decreasing the endothelium-dependent vasodilation, nitric oxide availability and the collateral coronary circulation[28-31]. The decrease in nitric oxide and prostacyclin levels, or even the increase in vasoconstrictors such as endothelin, are enhanced by hyperglycemia through protein kinase C activation, hexosamine increase and the activation of the pro-inflammatory nuclear factor Kappa B, with the consequent formation of superoxide radicals[32]. A study that induced diabetes in swine demonstrated an increase in IL-6, tumor necrosis factor (TNF), macrophage chemotactic proteins and adhesion molecules in fibroblasts of the coronary adventitia[33].

Regarding the leukocytosis, some studies explored its prognostic value in AMI[34]. One of the most relevant ones included leukocytosis as part of a risk score for infarcted patients[34]. In this study, men with leukocyte levels > 9,000/

Table 4 - Long-term prognostic value of the analyzed variables: multivariate analysis for the general population

Variables	t-ratio	P
Leukocytes	3,35	0.001
Glycemia (mg/dl)	1,75	0.08
Age	7,82	<0.001
EF (%)	-4,67	<0.001
History of HF	2,20	0.028
SAP	-3,58	<0.001

EF - ejection fraction; HF - heart failure; SAP - systolic arterial pressure.

Table 5 - Long-term prognostic value of the analyzed variables, excluding intrahospital deaths: univariate analysis

Variables	t-ratio	p
Leukocytes	0.01	0.989
Glycemia (mg/dl)	1.46	0.144

Table 6 - Long-term prognostic value of the analyzed variables, excluding intrahospital deaths: multivariate analysis

Variables	t-ratio	p
History of HF	2,18	0.029
Age	5,02	<0.001
FE (%)	-3,52	<0.001

HF - heart failure; EF - ejection fraction.

microL presented a relative risk of death of 1.66 (1.35-2.05) during the 4-year follow-up. Recently, the leukocytosis in patients with AMI was directly associated with the infarction area size, presence of shock and death in six months[34]. In another study, patients with leukocyte levels > 10,000 microL during AMI presented a higher incidence of TIMI 0/1 flow, adverse cardiovascular events, both intrahospital and throughout five years, in comparison with patients with leukocyte levels below this range[35]. The increase in neutrophil levels was also associated not only to the late treatment and the presence of occluded artery, but also to the decreased reperfusion in patients with AMI[36]. When compared to other inflammatory markers, the increase in leukocyte levels was a predictor of adverse events similar to C-reactive protein and a better predictor than the serum amyloid A, fibrinogen and interleukin-6, throughout five years after the AMI[37].

In our study, leukocytosis was associated to a worse intrahospital prognosis, even in adjusted models. However, as it occurred with hyperglycemia, during the long-term follow-up, when the intrahospital deaths are excluded, leukocytosis was no longer a long-term poor prognostic marker. The higher impact of this marker during the acute phase of AMI can be justified by the association of leukocytosis with increased acute inflammatory states, presence of more significant ischemia and difficulty in reperfusion, as mentioned before[36,37].

Finally, it is worth mentioning that, despite the evidence that the adequate control of glycemia in the acute phase of AMI is beneficial[11,38], the careful control of hyperglycemia is neglected in many institutions. On the other hand, attempts to control the inflammatory process have been reported with conflicting results in the literature[39]. Although a small study had initially pointed out a possible benefit with the use of anti-inflammatory agents in UMIS[40], the excess of cardiovascular events associated to the use of non-hormonal anti-inflammatory agents in several randomized studies discouraged the use of this treatment[41]. The control of inflammation was also investigated considering the use of statins in UMIS. In the last years, the pleiotropic effects of these drugs have been extensively investigated, especially the anti-inflammatory action. In this sense, a recent study demonstrated the efficiency of the decrease in C-reactive protein and LDL-cholesterol in patients with UMIS, without using high doses of atorvastatin. Moreover, there was an additional cardiovascular benefit in the group of patients with higher inflammatory reduction[42-44].

In conclusion, leukocyte and glycemia levels at the hospital admission of patients with AMI are excellent predictors of intrahospital mortality and poor predictors of long-term death. A previous history of HF was an independent predictor of mortality only at long-term. On the other hand, age and EF are short- and long-term independent predictors of mortality.

Potential Conflict of Interest

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

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Study Association

This study is not associated with any post-graduation program.

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