Do Diabetic Patients with Acute Coronary Syndromes Have a Higher Threshold for Ischemic Pain?

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Abstract

Background: **Data from over 4 decades have reported a higher incidence of silent infarction among patients with diabetes mellitus (DM), but recent publications have shown conflicting results regarding the correlation between DM and presence of pain in patients with acute coronary syndromes (ACS).**

Objective: **Our primary objective was to analyze the association between DM and precordial pain at hospital arrival. Secondary analyses evaluated the association between hyperglycemia and precordial pain at presentation, and the subgroup of patients presenting within 6 hours of symptom onset.**

Methods: **We analyzed a prospectively designed registry of 3,544 patients with ACS admitted to a Coronary Care Unit of a tertiary hospital. We developed multivariable models to adjust for potential confounders.**

Results: **Patients with precordial pain were less likely to have DM (30.3%) than those without pain (34.0%; unadjusted p = 0.029), but this difference was not significant after multivariable adjustment, for the global population (p = 0.84), and for subset of patients that presented within 6 hours from symptom onset (p = 0.51). In contrast, precordial pain was more likely among patients with hyperglycemia (41.2% vs 37.0% without hyperglycemia, p = 0.035) in the overall population and also among those who presented within 6 hours (41.6% vs. 32.3%, p = 0.001). Adjusted models showed an independent association between hyperglycemia and pain at presentation, especially among patients who presented within 6 hours (OR = 1.41, p = 0.008).**

Conclusion: **In this non-selected ACS population, there was no correlation between DM and hospital presentation without precordial pain. Moreover, hyperglycemia correlated significantly with pain at presentation, especially in the population that arrived within 6 hours from symptom onset. (Arq Bras Cardiol. 2014; 103(3):183-191)**

Keywords: **Diabetes Mellitus; Acute Coronary Syndrome; Chest Pain; Hyperglycemia.**

Introduction

Since the 1960's several investigators have reported a correlation between the presence of diabetes mellitus (DM) and a higher threshold for ischemic pain[1,2]. Necropsy data demonstrated a higher incidence of lesions at afferent nerves that conduct pain[3], supporting the hypothesis that patients with DM have impaired sensation of precordial pain. However, subsequent clinical data have provided conflicting results[4-12].

For example, in analyses of patients undergoing exercise stress testing and 48-hour continuous electrocardiographic monitoring to evaluate ischemia, Caracciolo et al.[5] found a similar prevalence of asymptomatic ischemia using both modalities in diabetics compared with non-diabetics. Meanwhile, Falcone et al[6] found an even higher incidence of angina during daily activities in patients with DM, while others reported a higher prevalence of *painless* ischemia among patients with DM[7].

Another method to explore the association between DM and symptomatic ischemia is to analyze the rate of unrecognized (silent) myocardial infarction in longitudinal studies. The majority of the publications report an absence of correlation between the presence of DM and silent MI, even when taking into account the presence of diabetic neuropathy[8-11]. These findings led Sheffer et al. to comment in a review of the topic that, "none of the existing epidemiologic analyses have identified diabetes as an independent predictor of infarct recognition"[12].

Analyses of the presence of chest pain at hospital arrival in patients with or without diabetes with acute coronary syndromes (ACS) represent a third opportunity to explore this question –

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results to date have been conflicting[13,14]. Since hyperglycemia is a strong predictor of in-hospital mortality[15-18], and admission with ACS often represents the unmasking of previously undiagnosed DM[19], exploration of the association between hyperglycemia at presentation and presence or absence of pain with ACS represents another venue to explore this issue.

The main purpose of this study was to analyze the associations between prior diabetes and the presence or absence of precordial pain in patients presenting at the hospital with ACS. The secondary aims included exploring the association between hyperglycemia and precordial pain, as well as analyzing the same associations in the subgroup of patients arriving at the hospital within 6 hours of symptom onset.

Methods

We analyzed data from a cohort of 3544 consecutive non-selected patients with ACS (1405 with ST-segment elevation myocardial infarction (STEMI), 1425 with non-STEMI, and 724 unstable angina) from a prospective registry of patients admitted to a coronary care unit of a tertiary hospital from 02/1998 to 04/2012. The registry included patients whose symptom onset started within 7 days, and included patients who were transferred from another hospital. We have used standard definitions to diagnose AMI as described in the concurrent guidelines, with measurement of creatine-kinase myocardial band (CK-MB) mass and cardiac troponin I on a routine basis from 2001 onward.

The presence of precordial pain at hospital arrival was determined by review of the patient's information obtained by the admitting physician(s) in the coronary care unit. Patient who were unconscious or disoriented were excluded. Patients who experienced other symptoms, such as dyspnea, fatigue, or other "ischemic equivalents" were classified as not having precordial pain. We defined the presence of diabetes mellitus from the medical history and/or use of glucose lowering drugs. Patients who had newly diagnosed diabetes during hospitalization were classified as not having diabetes at presentation. We defined hyperglycemia as the presence of a blood glucose level of > 125 mg/dL measured in the local hospital laboratory on the first measurement after hospital arrival.

Statistical analyses

The Chi-square and Fisher exact test were used for the comparison between categorical variables as appropriate. The Mann-Whitney (non-normal distribution, as determined by the Kolmogorov-Smirnov test) or Student's *t*-test (normal distribution) was used for comparisons between continuous variables.

Model development

Several adjusted models were developed to analyze the association between history of diabetes or hyperglycemia and presence of absence of pain at hospital arrival, using the backward stepwise logistic regression method. Those variables were chosen to develop a broad scenario regarding patient information at hospital arrival. The first 3 models tested the correlation between history of diabetes and pain at hospital arrival. Model 1A included as independent variables those listed in Table 1, except time from symptom onset and hyperglycemia. Model 1B included the same variables, plus time from symptom onset (as a continuous variable). Finally, model 1C was similar to model 1A, but was restricted to the population arriving at the hospital within 6 hours of symptom onset. Because history of diabetes was excluded in the first steps of the development of models 1A, 1B and 1C, similar additional models were developed, forcing the variable (history of diabetes) into the model. In order to analyze the association between hyperglycemia and pain at hospital arrival, we substituted history of diabetes by hyperglycemia in models 1A, 1B and 1C, generating models 2A, 2B and 2C respectively. Because hyperglycemia was excluded in the early steps of model 2A development, an additional model forcing the variable hyperglycemia until the last step was developed.

SPSS version 20.0 software (IBM, USA) was used for the analyses and a p-value < 0.05 (2-tailed) was considered statistically significant, with no corrections for multiple comparisons.

Results

The characteristics of the population are shown in Table 1. The mean age was 64.1 years and 68.6% were men. As commonly seen in tertiary hospitals, the incidence of risk factors was high, including 31.5% with known diabetes. As expected, significant differences were observed between the groups with *vs*. without precordial pain. For example, patients in the painless group were older and more likely to be smokers; on the other hand, this group had lower rates of previous heart failure, hypertension, coronary artery bypass graft surgery and were less likely to present with STEMI.

Figure 1 shows the unadjusted associations between a history of diabetes and presence of precordial pain at hospital arrival in the overall population (diabetes present in 30.3% with *vs*. 34.0% without pain, p = 0.029), as well as the subgroup who presented within 6 hours of symptom onset (30.2% vs 31.8%, p = 0.51).

There was no significant correlation between the presence of pain and in-hospital deaths (overall population: 8.8% for the painless group *vs*. 8.0% for the group with precordial pain, p = 0.44; subgroup within 6 hours from symptom onset: 7.6% *vs*. 7.2%, p = 0.74). Meanwhile, there was a higher rate of in-hospital mortality among patients with history of diabetes (overall population: DM 10.1% vs 7.4% for no DM, p = 0.006; subgroup within 6 hours of symptom onset 9.5% vs. 6.3%, p = 0.010).

Table 2 shows the variables that independently correlated with the presence of pain at hospital arrival in models 1A, 1B and 1C. Notably, a history of diabetes was not a significant predictor in any of the 3 models, with ORs of 0.97 (p = 0.67), 0.98 (p = 0.84) and 1.04 (p = 0.72), respectively when forced into models 1A, 1B and 1C. Figure 2 depicts the unadjusted and adjusted odds-ratios for the correlation between a history of diabetes and the presence of pain at hospital arrival.

Table 1 – Comparison between patients with or without chest pain at hospital arrival

Variable	Total	Without CP	With CP	OR (95% CI)	p-value
N (%) of patients	3544 (100)	1154 (32.6)	2390 (67.4)		
Mean age (SE), y	64.0 (0.21)	65.7 (0.37)	63.3 (0.26)		< 0.001
Male gender (%)	68.6	65	70.3	1.28 (1.10-1.48)	0.001
Caucasians (%)	86.3	86.0	86.4	1.03 (0.84-1.26)	0.801
History of Angina (%)	35.5	34.1	36.1	1.09 (0.94-1.26)	0.252
Hypercholesterolemia	56.2	58.0	55.4	0.90 (0.78-1.04)	0.148
Family with CAD	26.7	23.3	28.3	1.30 (1.10-1.53)	0.002
Diabetes	31.5	34.0	30.3	0.85 (0.73-0.98)	0.029
Hypertension	74.5	79.0	72.4	0.70 (0.59-0.82)	< 0.001
STEMI (%)	39.7	23.9	47.3	2.87 (2.45-3.35)	< 0.001
Mean time - symptom onset to hospital arrival (SE), h*	9.2 (0.49)	14.2 (1.15)	7.3 (0.51)	2.11 (1.78-2.49)	< 0.001
Symptom onset to hospital arrival ≤ 6h (%)	70.4	22.7	77.3	2.11 (1.78-2.49)	< 0.001
Mean glucose level at hospital arrival (SE), mg/dL**	137.87 (1.30)	135.9 (2.2)	139.2 (1.6)	1.19 (1.01-1.40)	0.072
Hyperglycemia (%)	39.9	37.0	41.2	1.19 (1.01-1.40)	0.035
Prior PCI (%)	21	22.2	20.4	0.90 (0.76-1.06)	0.218
Prior CABG (%)	18.1	21.8	16.4	0.70 (0.59-0.84)	< 0.001
Prior AMI (%)	32.5	33.0	32.3	0.97 (0.83-1.12)	0.652
Prior Stroke (%)	4.9	4.4	5.1	1.17 (0.84-1.64)	0.348
Prior Heart failure (%)	9.0	12.7	8.7	0.65 (0.53-0.65)	< 0.001
Current smoker (%)	23.7	19.4	25.7	1.44 (1.21-1.71)	< 0.001

(*)N = 3040; (**)N = 2867
CP: Chest Pain; OR: Odds-Ratio; CI: Confidence Interval; CAD: Coronary Artery Disease; STEMI- ST: elevation myocardial infarction; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Graft; AMI: Acute Myocardial Infarction.

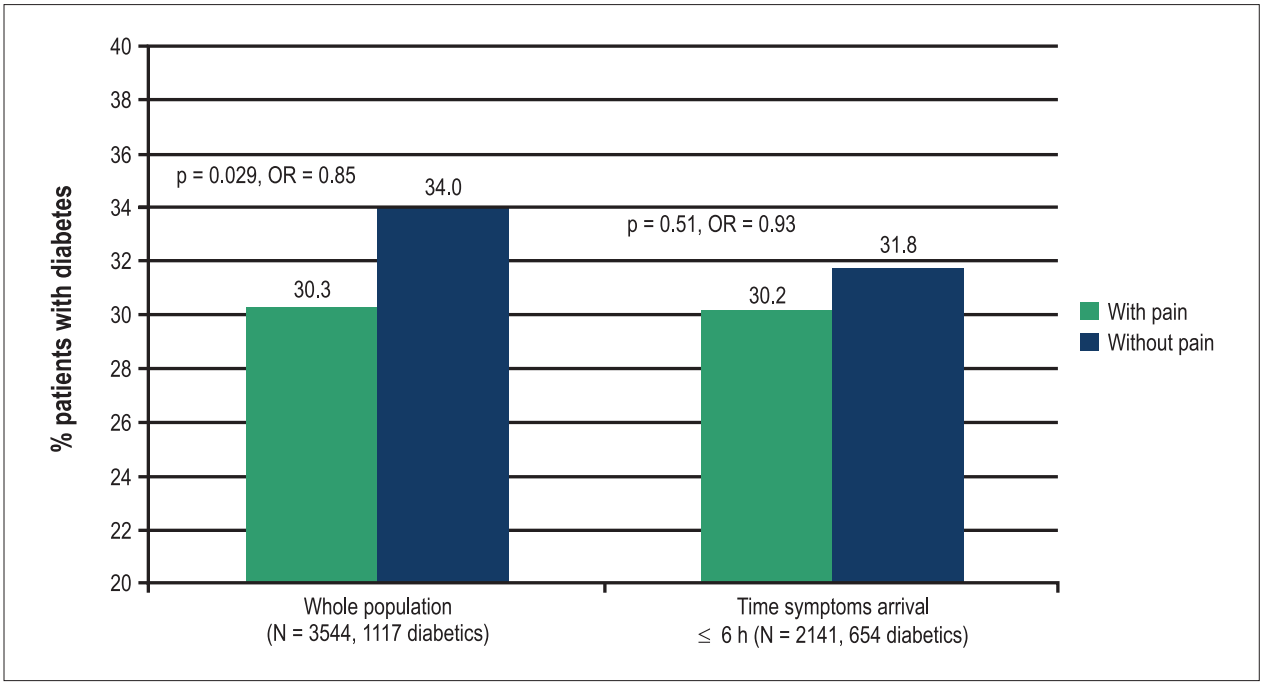

Figure 1 – *Prevalence of diabetes mellitus according to the presence or absence of pain at hospital arrival. Patients presenting with pain (dark bars) were slightly less likely to have diabetes among the overall population, but the same was not true among those who presented within 6 hours of symptom onset.*

Table 2 – Variables that were significantly and independently correlated with presence of chest pain at hospital arrival*

Variable	Adj. OR. (95% CI)	p-value
STEMI	2.91 (2.46-3.43)	< 0.001
History of angina	1.33 (1.14-1.56)	0.001
Age (per year)	0.99 (0.98-1.00)	0.004
Previous myocardial infarction	1.21 (1.03-1.43)	0.019
History of heart failure	0.77 (0.60-0.98)	0.032
History of arterial hypertension	0.83 (0.69-0.99)	0.038
Variable	**Adj. OR (95% CI)**	**p-value**
STEMI	2.76 (2.28-3.34)	< 0.001
Time from symptom onset < 6h	1.89 (1.59-2.25)	< 0.001
History of angina	1.42 (1.19-1.70)	<0.001
Previous myocardial infarction	1.33 (1.09-1.62)	0.004
Age (per year)	0.99 (0.98-1.00)	0.033
Variable	**OR adj. (95% CI)**	**p-value**
STEMI	3.07(2.43-3.87)	< 0.001
History of angina	1.37 (1.09-1.71)	0.006
Age (per year)	0.99 (0.98-1.00)	0.017

A- Included the baseline variables except time from symptom onset (see text); B- Adding time from symptom onset; C- Subgroup with time from symptom onset ≤ 6h; adj OR:- adjusted Odds-Ratio; CI: confidence interval; STEMI: ST-elevation myocardial infarction.

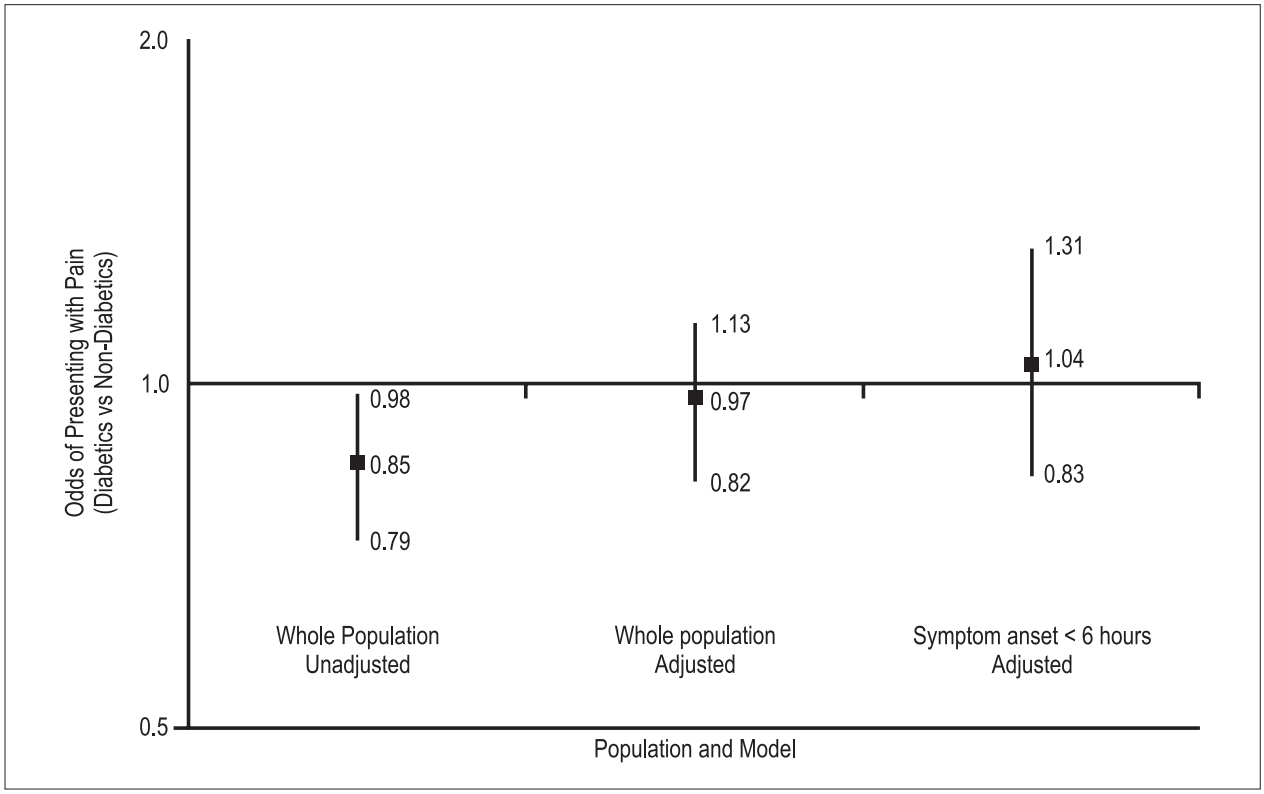

Figure 2 – *Correlation between history of diabetes and presence of pain at hospital arrival. In adjusted models, the presence of diabetes was not associated with the presence of pain at hospital presentation in either the overall population, or among the subgroup who presented within 6 hours of symptom onset.*

There was a significant correlation (unadjusted) between hyperglycemia at presentation and the presence of precordial pain at hospital arrival in the overall population and also in the subgroup that arrived in the hospital within 6 hours of symptom onset (Figure 3). Moreover, hyperglycemia was associated with a significantly higher rate of in-hospital mortality: 13.9% *vs*. 5.0% for patients with *vs*. without hyperglycemia (OR = 3.07, $p < 0.001$) for the overall population and 12.9% *vs*. 4.1% (OR = 3.43, $p < 0.001$) for those within 6 hours of symptom onset. Finally, hyperglycemia was significantly associated with STEMI (OR = 1.53, $p < 0.001$), presence of precordial pain at hospital arrival (OR = 1.49, $p = 0.001$) and history of diabetes (OR = 7.44, $p < 0.001$).

In the three adjusted models (Table 3), there was a positive correlation between hyperglycemia and presence of precordial pain in models 2B and 2C, but not in 2A, where the OR for hyperglycemia was 1.14 ($p = 0.14$). Figure 4 shows the unadjusted and adjusted odds-ratios for the association between hyperglycemia and presence of precordial pain at hospital arrival. Overall, considering all 6 models developed, the variables that best correlated with the presence of precordial pain at hospital arrival were presentation with STEMI and previous angina (significant correlation in all the 6 models), while older age and prior MI were significant correlated with precordial pain in 5 out of the 6 models.

Discussion

We showed in this analysis of 3544 consecutive and unselected patients with ACS admitted to the coronary care unit of a tertiary hospital that:

(1) A history of DM was not independently associated with precordial pain at hospital arrival in any of the adjusted models;

(2) The presence of hyperglycemia was independently correlated with precordial pain in 2 of the 3 adjusted models;

(3) Presentation with STEMI and a prior history of angina were most strongly associated with presentation with precordial pain at hospital arrival.

Potential causes of blunted perception of ACS in patients with DM include receptor and afferent neuron dysfunction, gating mechanisms and neuropsychiatric factors. While autonomic neuropathy has been proposed by some as the possible explanation for the relatively high incidence of painless ischemia in diabetic patients[3], others have failed to demonstrate cardiac denervation in patients with DM[20]. As noted by Sheifer et al[12], diabetic neuropathy may impair recognition of pain, but significant neurological dysfunction typically appears only in patients with advanced disease.

In 1973, Margolis et a[8] published their classic paper, showing that out of 259 patients with electrocardiographically documented MI, 23% were discovered only by routine ECG at the time of the patient's bi-annual routine examination. Moreover, they showed that unrecognized MI is rare in patients with prior angina pectoris and despite a numerically higher incidence in patients with diabetes or hypertension, the difference did not reach statistical significance[8]. In 1995 Sigurdsson et al[10] obtained similar results: at least one third of all MI were unrecognized, there was a strong correlation between absence of angina and unrecognized MI and risk factor profiles were similar in recognized or unrecognized MI. In a recently published review, the prevalence of silent MI in the general population varied from 22% to 64% and from 29% to 79% in diabetic patients[11].

Specifically among patients with acute myocardial infarction, 33% of patients did not have precordial pain in a North-American registry (National Registry of Myocardial Infarction 2)[13], while the incidence was much lower (10%) in a report from South Korea[21]. However, it is noteworthy that this difference could be explained, at least in part, by the fact that the South Korean registry included only patients with STEMI undergoing primary PCI, whereas the North-American registry included an unselected population of AMI patients. The present study was more similar to the North-American registry in that we analyzed data from an unselected population, and indeed found a similar percentage of patients who did not experience precordial pain (32.7%).

We did not find a strong correlation between the absence of precordial pain and diabetes in our registry of patients with ACS. Similar findings were first described by Christensen et al in 1985[22] in a population of patients with AMI, and were subsequently replicated in recent registries[14]. However, the aforementioned North-American registry did find a significant and independent association between the absence of precordial pain and presence of diabetes (adjusted OR 1.21, 95% CI 1.19-1.23)[13], contrary to the findings in our study and the others described above. Importantly, the North American registry did not adjust for STEMI as a potential confounder, despite the strong correlation between the presence of precordial pain and presentation with STEMI.

To the best of our knowledge, our analysis is one of the first to report the association between hyperglycemia at presentation and the presence of precordial pain. We found a positive correlation, especially for patients arriving to the hospital within 6 hours from symptom onset. One possible explanation for the finding could be related to the highly significant correlation between hyperglycemia at presentation and STEMI, the most acute of all manifestations of coronary artery disease.

We recognize several limitations to our analyses. First, although the registry sample was prospectively collected, the present analyses were retrospective and, therefore, they have the limitations of this type of clinical investigation. Secondly, only one question regarding the presence or absence of precordial pain at hospital arrival was ascertained in the dataset, with no information obtained regarding other symptoms such as dyspnea, nausea, syncope, fatigue or regarding the characteristics of the pain. Thirdly, we did not collect information on the type of diabetic therapy; however, it is important to note that Kentsch et al[14] did not find any correlation between the use of insulin and presence of angina. Lastly, we cannot exclude the possibility of bias in the selection of patients included in this registry, as one might expect a higher rate of hospitalization for patients who experience precordial pain compared with those without pain.

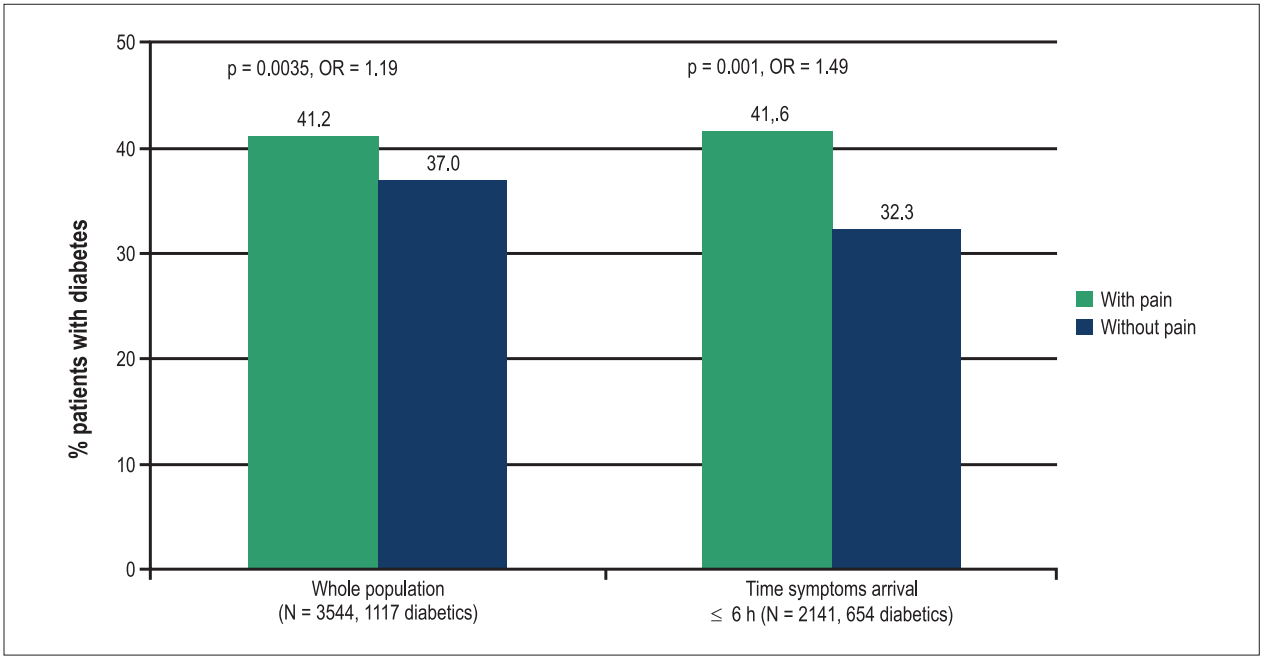

Figure 3 – *Incidence of hyperglycemia according to the presence or absence of pain at hospital arrival. Patients with hyperglycemia (dark bars), defined as first glucose level >125 mg/dL after hospital arrival, were more likely to present with pain compared with those without hyperglycemia in the overall population and also among those with symptom onset within 6 hours.*

Table 3 – Variables that were significantly and independently correlated with presence of chest pain at hospital arrival, substituting history of diabetes by glucose level at hospital arrival

Variable	OR adj. (95% CI)	p-value
STEMI	2.74 (2.28-3.30)	< 0.001
History of angina	1.33 (1.12-1.59)	0.001
History of stroke	1.85 (1.22-2.80)	0.004
Previous myocardial infarction	1.27 (1.06-1.53)	0.010
History of heart failure	0.71 (0.55-0.93)	0.014
Male gender	1.22 (1.02-1.45)	0.029
Family with CAD	1.23 (1.01-1.49)	0.034
Age (per year)	0.99 (0.97-1.00)	0.050
Variable	**Adj. OR (95% CI)**	**p-value**
STEMI	2.60 (2.10-3.21)	< 0.001
Time from symptom onset < 6h	1.99 (1.64-2.42)	< 0.001
History of angina	1.42 (1.16-1.74)	0.001
Previous myocardial infarction	1.37 (1.11-2.92)	0.004
History of heart failure	0.67 (0.49-0.91)	0.011
Previous stroke	1.81 (1.12-2.92)	0.015
Age (per year)	0.99 (0.98-1.00)	0.033
Variable	**Adj. OR(95% CI)**	**p-value**
STEMI	2.99 (2.30-3.89)	< 0.001
Previous myocardial infarction	1.52 (1.16-1.97)	0.003
History of stroke	2.33 (1.13-4.78)	0.022
History of angina	1.30 (1.01-1.67)	0.044
Smoking	1.35 (1.01-1.80)	0.045

Included the baseline variables except time from symptom onset (see text); B- Adding time from symptoms onset; C- Subgroup with time from symptoms onset ≤ 6h; adj OR: adjusted Odds-Ratio; CI: confidence interval; STEMI: ST-elevation myocardial infarction.

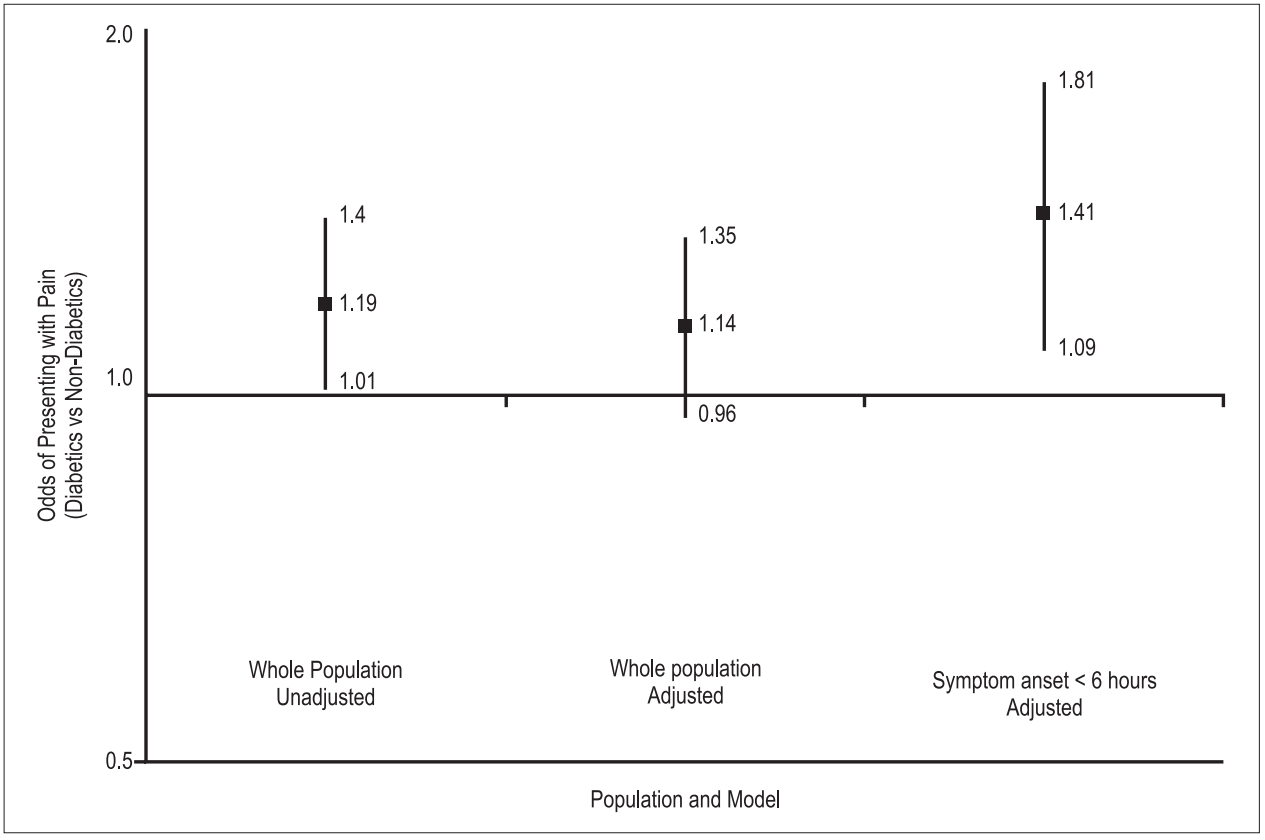

Figure 4 – *Correlation between hyperglycemia and presence of pain at hospital arrival. In adjusted models, patients with hyperglycemia were not more likely to present with pain in the total population. However, among those who had symptom onset within 6 hours, there was a 41% increase in the odds of presenting with pain compared with those without hyperglycemia after multivariable adjustment.*

Conclusion

The present study suggests that, contrary to what has been deemed "common knowledge" for several decades, the presence of diabetes did not correlate independently with a higher likelihood of absence of precordial pain in this registry of patients presenting with ACS at a tertiary medical center. In addition, we found that acute-phase hyperglycemia is more common in patients presenting with precordial pain, particularly when they present within 6 hours from symptom onset. Patients with STEMI and those who have a prior history of angina are more likely to present with precordial pain at the time of presentation with AMI.

Author contributions

Conception and design of the research, Analysis and interpretation of the data and Writing of the manuscript: Nicolau JC, Giugliano RP; Acquisition of data and Statistical analysis: Nicolau JC; Critical revision of the manuscript for intellectual content: Franci A, Barbosa CJDG, Baracioli LM, Franken M, Lima FG, Giraldez RR, Kalil Filho R, Ramires JAF.

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 thesis or dissertation work.

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