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Glycosylated hemoglobin and the risk of periprocedural myocardial infarction in non-diabetic patients

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ABSTRACT

Background: Alterations of glucose homeostasis have been reported to occur even in non-diabetic patients, thus increasing the risk of cardiovascular events and worsening the outcome after an acute myocardial infarction (AMI). Still debated is the role of impaired glucose control in patients undergoing percutaneous coronary intervention (PCI), as hyperglycemia, represents an important pro-thrombotic stimulus, increasing platelet reactivity and potentially procedural complications. Therefore, the aim of our study was to assess the association between glycosylated hemoglobin and periprocedural myocardial infarction (PMI) in non-diabetic patients undergoing PCI.

Methods: We included patients without history of diabetes undergoing elective PCI. PMI was defined as creatine kinase-MB increase by 3 times the upper limit normal or by 50% of an elevated baseline value, whereas periprocedural myonecrosis as Troponin I increase by 3× ULN or 50% of baseline.

Results: Our population is represented by 1199 patients, who were divided according to tertile values of glycosylated hemoglobin (HbA1c). Higher HbA1c was associated with ageing ($p < 0.001$), hypertension ($p = 0.005$), previous myocardial infarction ($p = 0.009$), PCI ($p < 0.001$) or CABG ($p = 0.001$), treatment with diuretics ($p < 0.001$), higher levels of glycemia ($p < 0.001$) and white blood cells ($p = 0.02$), multivessel coronary artery disease ($p = 0.03$), higher rate of instent restenosis ($p = 0.02$).

HbA1c did not impact on periprocedural myocardial infarction ($p = 0.85$; adjusted OR [95% CI] = 0.91 [0.74–1.12], $p = 0.38$) or myonecrosis ($p = 0.69$; adjusted OR [95% CI] = 0.95 [0.80–1.13], $p = 0.56$). Similar results were obtained fasting glycemia for PMI ($p = 0.82$, adjusted OR [95% CI] = 0.90 [0.71–1.14], $p = 0.37$) and myonecrosis ($p = 0.21$, adjusted OR [95% CI] = 1.02 [0.84–1.24], $p = 0.84$) and confirmed in high-risk subsets of patients.

Conclusions: In non-diabetic patients undergoing elective PCI, neither glycosylated hemoglobin levels nor fasting glycemia are associated with the risk of periprocedural myocardial infarction and necrosis.

1. Background

Many improvements have been obtained in percutaneous coronary interventions (PCI), especially in the setting of acute coronary syndromes, mainly due to the availability of better antithrombotic therapies and mechanical devices, that allow the percutaneous treatment of more complex lesions (De Luca, Cassetti, & Marino, 2009; De Luca, Verdoia, & Suryapranata, 2012; Navarese et al., 2011; Palmerini et al., 2014). However still suboptimal results are observed in certain high-risk patients (De Luca et al., 2009; Kocas et al., 2014; Piccolo et al., 2014), with up to 20% of procedures being complicated by a periprocedural myocardial injury or MI (Califf et al., 1998). Myocardial damage after PCI, appearing as a postprocedural raise in cardiac enzymes, often occurs after complications impairing the flow in epicardial coronary vessels, such as distal embolization, side branch loss or dissections. However, also silent thrombotic obstruction of coronary microcirculation has been claimed for these events, thus recognizing a central role of enhanced platelet reactivity or pro-thrombotic status (Cuculi, Lim, & Banning, 2010; Desai & Bhatt, 2010; Hanna & Hennebry, 2010).

Hyperglycemia has emerged in the last years as the major determinant for the higher cardiovascular risk of diabetics, inducing inflammation, platelet hyper reactivity and endothelial dysfunction (Ferreiro & Angiolillo, 2011). Moreover, glycemic peaks have been reported to negatively impact on prognosis in patients with acute MI undergoing primary PCI, regardless of the diabetic status (Deckers, van Domburg, Akkerhuis, & Nauta, 2013). However, alterations of glucose metabolism beyond the "diabetic" threshold have been

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recently linked with cardiovascular morbidity and mortality in patients without diabetes mellitus (Fisman et al., 2001), and higher values, within normal range, of glycosylated hemoglobin, a parameter of chronic glucose control, have been associated to a poorer outcome after PCI in non-diabetics (Corpus, O'Neill, Dixon, Timmis, & Devlin, 2003).

However, few data have been collected on the relationship between glucose homeostasis parameters and procedural outcome after an elective PCI in non-diabetics. Therefore, the aim of our study was to evaluate the association between glycosylated hemoglobin and periprocedural MI in patients without diabetes mellitus undergoing non-urgent PCI.

2. Methods

We included patients without a previous history of diabetes (American Diabetes Association, 2009) at admission undergoing percutaneous coronary interventions at Ospedale "Maggiore della Carità" from May 2007 to January 2013 for both elective indication or acute coronary syndrome/NSTEMI (ACS). NSTEMI patients were defined by the presence of chest pain and cardiac biomarkers elevation > ULN (respectively 0.04 μg/l for Troponin I and 5.00 μg/l for CK-MB) undergoing elective coronary angiography after pharmacological stabilization. STEMI and unstable patients requiring urgent coronary revascularization were excluded.

Hypertension was defined as systolic pressure > 140 mmHg and/or diastolic pressure > 90 mmHg or if the individual was on treatment with antihypertensive medications.

The study was approved by our Institutional Ethical Committee of Novara. All patients received, according to guidelines, high-dose bolus of clopidogrel (600 mg) at the time of hospitalization or before angioplasty. Patients were clinically followed up to hospital discharge.

2.1. Biochemical measurements

Blood samples were drawn at admission in patients undergoing elective (following a fasting period of 12 h) or urgent coronary angiography. Glucose, creatinine, HbA1c and lipid profile were determined by standard methods as previously described (De Luca et al., 2012). All blood samples were analyzed within 2 h of venepuncture. Cardiac biomarkers (Troponin I and CK MB) were measured at baseline, before coronary revascularization, and later 6, 12, 24 and 48 h after PCI.

2.2. Coronary angiography and PCI

Coronary angiography was routinely performed by the Judkins technique using 6-French catheters. Quantitative coronary angiography was performed by experienced interventional cardiologists by an automatic edge-detection systems (Siemens Acom Quantcor QCA, Erlangen, Germany) (Verdoia et al., 2013). Coronary angioplasty was performed with standard techniques. Use of stents, type of stents and stent implantation techniques, as much as the use of directional or rotational atherectomy, IVUS, glycoprotein IIb–IIIa inhibitors, was left at the discretion of the operators.

2.3. Study endpoints

Primary study endpoint was periprocedural MI defined as CK-MB mass release ≥ 3 times the upper limit normal (ULN) or an increase by 50% of baseline if already elevated, but stable or falling, at the time of the procedure. Secondary study endpoint was periprocedural increase in troponin I ≥ 3× ULN or an increase by 50% of the pre-procedural value, if > 0.04 ng/ml.

Table 1
Clinical and demographic features according to HbA1c tertiles values.

Baseline clinical characteristics	≤5.6% N = 422	5.61–6% N = 414	>6% N = 363	p value
Age (mean ± SD)	65.1 ± 12.2	67.6 ± 10.9	69.4 ± 11.4	<0.001
Male sex (%)	78.2	76.8	78	0.92
Hypertension (%)	62.5	71	71.6	0.005
Hypercholesterolemia (%)	52.7	61	57.3	0.17
Smokers (%)				0.88
Active smokers	30.7	28.4	22.4	
Previous smoker	24.3	27.4	27.9	
Renal failure (%)	20.7	24.5	22.7	0.48
History of MI (%)	21.6	26	29.8	0.009
Previous PCI (%)	24.2	26.5	35.9	<0.001
Previous CABG (%)	9.7	10.4	17.6	0.001
Indication to angiography (%)				0.74
Stable angina	20.8	21	25.7	
Acute coronary syndrome	76.6	74.2	68.3	
LV dysfunction/Arrhythmia	2.5	4.8	6	
Therapy at admission				
ACE inhibitors (%)	41.7	38.5	48	0.11
ARB (%)	17.7	17.9	20.3	0.41
Beta blockers (%)	56.4	55.9	57.6	0.76
Nitrates (%)	41.5	42.8	45.5	0.30
Calcium antagonists (%)	20.1	27	22.2	0.51
Diuretics (%)	17.4	27.4	32	<0.001
Statins (%)	53	59.8	57.9	0.18
ASA (%)	66	67.3	66.5	0.88
Clopidogrel (%)	33.3	32.2	29.6	0.3
Main chemistry				
Glycemia (mg/dl ± SD)	107.4 ± 20.6	111.7 ± 23.5	121.9 ± 35.1	<0.001
Creatinine (mg/dL ± SD)	1.1 ± 0.9	1.1 ± 0.7	1.1 ± 0.7	0.96
Platelets (10^3/μl; mean ± SD)	210.1 ± 57.4	219.4 ± 72.7	215.5 ± 57.7	0.16
Hemoglobin (g/dl ± SD)	13.6 ± 1.8	13.5 ± 1.7	13.4 ± 1.6	0.18
WBC (10^3/μl; mean ± SD)	7.8 ± 2.7	7.9 ± 2.4	8.3 ± 3.6	0.02
HDL cholesterol (mg/dl ± SD)	40.9 ± 12.2	40.3 ± 11	40.3 ± 11.9	0.66
LDL cholesterol (mg/dl ± SD)	99.7 ± 35.9	96.5 ± 37.2	93.9 ± 36.1	0.09