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Evaluation of the endothelial glycocalyx damage in patients with acute coronary syndrome

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ABSTRACT

Background: Endothelial glycocalyx (EG) is sugar-based cell-bound surface molecules linked to transmembrane proteins observed on the endothelial surface of the vessels. Damage to this structure causes an increase in platelet and leucocyte adhesion and shear stress in the vessel. We hypothesized a possible link between EG damage and acute coronary syndrome (ACS).
Methods: We measured the syndecan-1 levels (a biomarker of EG damage) in 141 patients (99 men) with ACS and compared to those of 45 patients (24 men) with non-coronary chest pain (NCCP) and of 24 (14 men) healthy individuals (CONTROL).
Results: The baseline characteristics of the ACS and NCCP groups were similar. Syndecan-1 levels were significantly higher in the ACS group than in the NCCP ($p = 0.01$) and CONTROL ($p = 0.001$) groups but did not differ between the NCCP and CONTROL groups ($p = 0.83$). In analysis according to gender category, the difference among the groups remained significant only for men ($p = 0.0009$). A syndecan-1 level higher than 148 ng/ml was associated with ACS diagnosis with an odds ratio of 14 (95% confidence interval (CI): 1.8 to 102), $p = 0.011$. After adjusting for gender, age and current or past tobacco use, this syndecan-1 level remained positively associated with ACS diagnosis with an odds ratio of 12 (95% CI: 1.6 to 93), $p = 0.016$.
Conclusion: Higher syndecan-1 levels were observed during ACS, mostly in men, suggesting that EG damage could participate in the atherosclerotic plaque vulnerability process in these patients.

1. Introduction

The endothelial glycocalyx (EG) is a sugar-based cell-bound surface molecules linked to transmembrane proteins observed on the endothelial surface of the blood vessels [1–3]. Damage to this structure is associated with an increase in platelet and leucocyte adhesion and in shear stress inside the vessel due to decreasing nitric oxide production [4–7]. The syndecan-1 is the most common transmembrane protein constituting of the EG, however is not an endothelial-cell specific protein. A soluble form is produced by the shedding of the EG, and its circulating levels are used as a biomarker of injury to this structure. Many cardiovascular risk factors can contribute to the EG shedding such as inflammation, diabetes, oxidized LDL, etc [8].

The rupture or erosion of atheromatous plaque is considered the main mechanism responsible for triggering acute coronary syndromes (ACS) [9]. The inflammation, thrombosis and increased shear stress inside the coronary artery are recognized factors leading to plaque instability [10]. We hypothesized a possible link between EG damage and the ACS occurrence.

2. Methods

2.1. Patients

Patients admitted to the emergency department of our hospital with a probable ACS diagnosis were included in the study. Patients were divided into two groups based on their diagnosis: acute coronary syndrome (ACS) and non-coronary chest pain (NCCP).

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The diagnosis of acute myocardial infarction (AMI) was based on the Third Universal Definition of Myocardial Infarction [11]. For this diagnosis we used the rise and/or fall of troponin level above the 99th percentile reference limit and with at least one of the following: symptoms of ischemia, new or presumed new significant ST-segment-T-wave changes or identification of an intracoronary thrombus by angiography. Compatible coronary angiography findings with ACS were used in all patients to establish a definite ACS diagnosis.

The group of non-coronary chest pain (NCCP) consisted of patients admitted because of chest pain and electrocardiogram without ischemic alterations plus a negative troponin I level associated with an invasive coronary angiography or coronary computed tomographic angiography without atherosclerotic lesions or a negative non-invasive exam (stress echocardiography, exercise electrocardiography or nuclear stress testing).

Exclusion criteria were: age less than 18 years, cardiac arrest or circulatory shock (systolic blood pressure less than 90 mm Hg) during pre-hospital phase or at admission, suspected infection, presence of chronic diseases such as heart failure, liver cirrhosis, cancer, renal insufficiency with creatinine higher than 2.5 mg/dl, and illicit drug use.

For comparison purposes, 24 healthy individuals (14 males, mean age 34 ± 07 years-old) were included in the CONTROL group. Asymptomatic individuals without any cardiovascular risk factors and who were not taking any medication constituted this group.

The Ethics Research Committee of our institution approved the study. All patients gave written informed consent.

2.2. Study design

A peripheral venous blood sample was obtained at admission to quantify syndecan-1 levels. Another such blood sample was obtained 12 h after the onset of chest pain to measure troponin I and C-reactive protein (CRP). In a subgroup of ACS patients, additional serial blood samples for the measurement of syndecan-1 levels were obtained 12 and 24 h after the onset of chest pain. Samples were centrifuged at 1000*g* for 10 min after clot formation and the serum collected was stored at −70 °C.

2.3. Measurement of syndecan-1, troponin I and CRP

Syndecan-1 (CD138) levels were measured by ELISA (Enzyme-Linked Immunosorbent Assay) using commercial kits (Abcam®, Cambridge, UK) according to manufacturer instructions. The sensitivity or minimum detectable level of syndecan-1 was 4.94 ng/ml. Troponin I levels were measured by ELFA (Enzyme-Linked Fluorescent Assay) using commercial kits (Vidas® Troponin I Ultra, bioMérieux, Lyon, France). C-reactive protein (CRP) levels were measured by the PETIA (Particle enhanced turbidimetric immunoassay) technique using commercial kits (RCRP Dimension®, Siemens, Newark, USA).

2.4. Statistical analysis

Fisher's exact test was used to compare categorical variables. The Student *t*-test was used to compare unpaired continuous variables with Gaussian distribution. For comparison of unpaired continuous variables with non-Gaussian distribution the Mann-Whitney test was used to compare two groups and the Kruskall-Wallis test with Dunn's post-test correction was used to compare three or more groups. The Friedman test with Dunn's post-test correction was used to compare paired continuous variables with non-Gaussian distribution. The Spearman correlation coefficient was used to determine the correlation between two continuous variables with non-Gaussian distribution. The syndecan-1 levels were expressed in median and percentiles (25th and 75th). Multivariate analysis was performed trough logistic regression adjusting the data for these variables: age, gender and current or past tobacco use. The Stata 13.1 software (College Station, TX, USA) was used for statistical analysis. The level of significance was set at $p < 0.05$ for all analyses.

3. Results

The characteristics of the patients included in the study are shown in Table 1. No differences in demographic or clinical characteristics were observed between the ACS and NCCP groups. Of the 141 patients in the group with ACS, 71 (50%) were diagnosed with ST-segment elevation AMI, 58 (41%) with non-ST-elevation AMI and 12 (09%) with unstable angina.

Syndecan-1 levels were significantly different among the three groups ($p = 0.002$) with higher levels in the ACS (77 ng/ml; 46–134) compared to the NCCP (60 ng/ml; 32–70), $p = 0.012$ and the CONTROL group (42 ng/ml, 27–80), $p = 0.001$. There was no difference between the NCCP and CONTROL groups, $p = 0.830$. When the analysis was performed according to gender category, the difference among the groups remained significant only for males, with syndecan-1 levels higher in the ACS (77 ng/ml; 47–135) compared to NCCP (60 ng/ml; 21–84) and the CONTROL groups (42 ng/ml; 31–61), $p = 0.0009$. However this association was not observed for females, with syndecan-1 levels similar among the three groups: ACS (62 ng/ml; 42–127), NCCP (60 ng/ml; 35–78) and CONTROL (44 ng/ml; 27–95), $p = 0.210$. Fig. 1.

A syndecan-1 level higher than 148 ng/ml (corresponding to the 99th percentile of the control group) was associated with ACS diagnosis with an odds ratio of 14 (95% confidence interval (CI): 1.8–102), $p = 0.011$. After multivariate logistic regression adjusting for gender, age and current or past tobacco use, this syndecan-1 level remained positively associated with ACS diagnosis with an odds ratio of 12 (95%CI: 1.6–93), $p = 0.016$.

Analysis according to type of presentation of the ACS revealed a higher level of syndecan-1 in patients with ST-segment elevation AMI (78 ng/ml; 53–175) compared to the group with unstable angina (48 ng/ml; 26–85), $p = 0.030$; however, there was no difference between ST-segment elevation AMI and non-ST-segment elevation AMI (77 ng/ml; 39–122), $p = 0.630$ or between unstable angina and non-ST-segment elevation AMI, $p = 0.210$.

Serial measurements of syndecan-1 levels were performed in 43 patients at admission, 12 and 24 h after the onset of chest pain (28 patients with ST-segment elevation AMI and 15 patients with non-ST-elevation AMI). The levels of this biomarker at admission in this subgroup were higher (78 ng/ml; 44–173) compared to the CONTROL group (42 ng/ml; 27–80), $p = 0.001$. Syndecan-1 levels increased after 12 h (124 ng/ml, 79–210) in relation to admission, $p = 0.005$, but no additional increase was observed at 24 h (128 ng/ml, 81–202), $p > 0.990$.

There was no significant correlation between syndecan-1 levels at admission and serum troponin I measured 12 h after the onset of symptoms ($r = 0.128$), $p = 0.147$. There was a weak correlation between syndecan-1 levels at admission and serum levels of C-reactive protein ($r = 0.200$), $p = 0.030$.

4. Discussion

The present study demonstrated that patients with ACS already had higher levels of syndecan-1 at admission than the group of patients with similar cardiovascular risk factors but without an ACS diagnosis, particularly in the male gender. Moreover, further acute elevation of this biomarker was detected during serial