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Association of circulating levels of neopterin with non-culprit plaque vulnerability in CAD patients an angiogram, optical coherent tomography and intravascular ultrasound study

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ABSTRACT

Background: Neopterin is a pteridine derivative secreted by activated macrophages. Previous studies have shown that neopterin plays a pivotal role in coronary artery disease (CAD); however, the relationship between circulating neopterin and non-culprit plaque vulnerability in patients with CAD remains unclear. In this study, we investigated the correlation of neopterin and vulnerable plaque features in patients with CAD.

Methods: One hundred and thirty non-culprit plaques from 81 patients with CAD were assessed by angiogram and optical coherence tomography (OCT) as well as intravascular ultrasound (IVUS) imaging. According to the median value of serum neopterin (10.61 nmol/L), patients were divided into a low neopterin group (n = 40, <median) and a high neopterin group (n = 41, ≥median). Plaque characteristics were compared between the two groups.

Results: Compared with the low neopterin group, OCT findings showed that patients in the high neopterin group had thinner fibrous cap thickness (FCT) (90.02 ± 52.96 μm vs. 124.69 ± 65.23 μm, $P = 0.004$) and more thin-cap fibroatheroma (TCFA) (38.0% vs. 13.6%, $P = 0.002$). Microvessel and plaque rupture were more frequently observed in the high neopterin group ($P = 0.004$ and $P = 0.005$, respectively). IVUS findings showed that plaque burden was greater in the high neopterin group than that in the low neopterin group ($P = 0.005$).

Conclusions: Neopterin was positively associated with vulnerable plaque features including TCFA, thinner fibrous cap, plaque rupture, greater plaque burden and frequent microvessel occurrence in CAD patients.

1. Introduction

Coronary artery disease (CAD) is categorized as an inflammatory condition. As a crucial inflammatory cell, macrophages play a pivotal role in atherosclerosis plaque progression and destabilization [1]. Activated macrophages release various pro-inflammatory factors, which contribute to weakening of the fibrous cap and expansion of the necrotic core, leading to plaque rupture and symptoms of acute coronary syndrome (ACS) [2].

Neopterin, a pterin derivative, is secreted by macrophages activated by interferon-γ. In a previous study, Liu et al. [3] found that neopterin was increased in patients with ACS but not in those with stable angina pectoris (SAP). Furthermore, neopterin was revealed as a predictor of future adverse cardiac events in patients with SAP and ACS [4,5]. Moreover, the PROVE IT–TIMI 22 trial has shown that elevated neopterin levels are a potent prognostic factor for patients at long-term risk of death or recurrent acute coronary events after ACS [6].

Increasing levels of neopterin were found to be associated with vulnerable plaques in a histological study [7]; however, the relationship between circulating levels of neopterin and plaque vulnerability in intravascular findings remains unclear. As an extensively applied intravascular imaging technology, intravascular ultrasound (IVUS) has the advantages of good penetration of tissue (10 mm) and accurate quantification of the atherosclerotic plaque

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burden. In recent years, optical coherence tomography (OCT) has emerged as one of the most promising technologies for the evaluation of crucial features of vulnerable plaques due to the benefit of high resolution (≤10 μm) [8]. In this study, we analyzed the coronary non-culprit plaque vulnerability by a combination of IVUS and OCT as well as angiogram, and explored its correlation with circulating neopterin levels in patients with CAD.

2. Methods

2.1. Patients

Venous blood of 81 consecutive patients hospitalized for angiogram were collected from January 2013 to May 2014. Written informed consent was obtained from each subject prior to enrollment, and the study was approved by the Ethics Review Committee at the Harbin Medical University (China). The inclusion criteria were as follows: a *de-novo* lesion with a luminal stenosis diameter between 30% and 70% in a non-culprit/non-target site, and ≥10 mm away from the culprit lesion. Invasive OCT and IVUS imaging was performed during the index procedure and the neopterin level of all patients was detected. Acute coronary syndrome (ACS) was defined as non-ST-elevated myocardial infarction (NSTEMI) or stable angina pectoris (SAP). NSTEMI was defined as an acute myocardial infarction with ECG changes other than ST segment elevation and at least one instance of elevated levels of cardiac enzymes indicative of myocardial necrosis. Unstable angina pectoris (UAP) was characterized by a progressive crescendo pattern or angina at rest without elevated levels of cardiac markers. Stable angina pectoris (SAP) was defined as effort-related angina without any change in clinical pattern in the preceding 2 months [9]. Patients were excluded from the study if they had (i) left main disease; (ii) chronic total occlusion; (iii) extremely tortuous or heavily calcified vessels; (iv) congestive heart failure with left ventricular ejection fraction <40%; or (v) renal insufficiency with serum creatinine >2.0 mg/dL; (vi) other inflammatory conditions including cancer, infection, and autoimmune disease.

2.2. Angiographic imaging

Coronary angiograms were recorded at identical projections that showed the stenosis at the most severe degree. Quantitative coronary angiographic (QCA) analysis was performed with a validated automated edge-detection algorithm (CAAS 5.10.1, Pie Medical Imaging BV. Maastricht, Netherlands). The angiogram variables included: the minimal lumen diameter (MLD), reference segment diameter (RD), lesion length and diameter of stenosis (DS).

2.3. OCT image acquisition and analysis

We adopted the Frequency Domain-OCT C7XR system for OCT image acquisition of the target vessels (LightLab Imaging). The OCT image analysis was performed by two independent observers using proprietary software (LightLab Imaging) and in accordance with the recently published consensus for qualitative and quantitative assessment [10]. Intra-luminal OCT derived parameters were assessed as previously described [11]. A fibrous cap was defined as a signal-rich homogenous region overlying a lipid core, characterized by a diffusely bordered signal-poor region. Fibrous cap thickness (FCT) was measured three times at the thinnest point of each plaque and the average was calculated. A microvessel was defined as a circular black region with a diameter of 50 μm–300 μm within a plaque that was present in at least three consecutive frames. A thin-cap fibroatheroma (TCFA) was defined as a lipid-rich plaque (maximum lipid arc >90°) with a fibrous cap <65 μm. The lipid arc was measured at 1 mm intervals throughout the entire length of the lipid plaque. Ruptured plaques were defined as a lipid plaque with fibrous cap discontinuity and cavity formation inside the plaque. A thrombus was defined as an irregular mass protruding into the lumen with a measured dimension ≥250 μm.

2.4. IVUS imaging and analysis

IVUS imaging was performed with an automated transducer pullback system and a scanner (Boston Scientific, Boston, USA). The IVUS images were recorded on a disk for subsequent study. For each plaque, the corresponding IVUS images were selected using distinctive points such as calcifications, branches and stents. As described previously [11], all IVUS images were analyzed using semi-automatic software (EchoPlaque, Index Systems, Mountain View, California) by two independent reviewers. A consensus reviewer was consulted in cases of discordance between the reviewers. The references for analysis were as follows: external elastic membrane (EEM), lumen cross-sectional area (CSA), plaque plus media (P + M) CSA. The remodeling index was calculated as (EEM CSA at the minimal lumen area intersection)/(average of the proximal and distal reference EEM CSA). The plaque burden was calculated as (P + M CSA/EEM CSA × 100%).

2.5. Measurement of neopterin

Venous blood samples from every patient were obtained at the time of hospital admission. Aliquots of serum were stored at −80 °C for later analysis. Serum levels of neopterin were measured by commercially available human neopterin enzyme-linked immunosorbent assay (ELISA) kit (R&D, Minneapolis, USA) according to the manufacturers' instructions. The OD value was detected using a microplate reader (BioTek, CA, USA).

2.6. Statistical analysis

All statistical analysis was performed with SPSS Statistics 19.0 (IBM Corp., Armonk, NY, USA). Categorical variables are expressed as n and percentage. Continuous variables are expressed as mean ± standard deviation. The data were analyzed on a per-patient basis for clinical characteristics and on a per-stenosis basis for lesion morphology. Continuous variables were compared using an independent sample *t*-test. Pearson's Chi-square test was used to compare categorical variables. $P < 0.05$ was considered to indicate statistical significance.

3. Results

3.1. Baseline characteristics of patients

According to the median value of neopterin levels (10.61 nmol/L), we divided the 81 enrolled patients into two groups: a low neopterin group (neopterin levels below the median) and a high neopterin group (neopterin level ≥the median). The low neopterin group comprised 40 patients with 59 non-culprit lesions and the high neopterin group comprised 41 patients with 71 non-culprit plaques. As shown in Table 1, no significant differences in age, sex and CAD risk factors were observed between the two groups ($P > 0.05$). However, as shown in Table 2, the glucose level of patients in the low neopterin group was slightly higher than those in the high neopterin group (6.91 ± 2.86 vs. 6.35 ± 1.74 mg/dL, $P = 0.023$). There was a significant difference between the neopterin levels in the low and high neopterin groups (6.45 ± 2.87 vs. 14.45 ± 2.03 nmo/L, $P < 0.001$), but there were no significant differences in the levels of other biomarkers.