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Serum IgE levels are associated with coronary artery disease severity

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ABSTRACT

Background and aims: Immunoglobulin E (IgE), a key element of allergic reactions, was considered to be involved in the development of atherosclerosis and the pathogenesis of myocardial ischemia. This study was designed to test whether total serum IgE levels were associated with the atherosclerosis severity of coronary artery disease (CAD).

Methods: Total serum IgE concentrations were measured in 708 consecutive patients who were presented to our center for coronary angiography. Atherosclerosis severity of CAD was assessed by the number of diseased vessels showing ≥50% diameter stenosis and quantified by Gensini score.

Results: Patients with CAD (N = 562) had higher serum IgE levels than those without CAD (N = 146) [55.90 (19.10–156.00) *vs.* 26.90 (11.80–62.10) KU/L, $p = 0.003$]. Furthermore, the serum IgE levels were significantly increased in patients with multivessel disease (MVD) compared to those with single-vessel disease [61.80 (23.20–159.00) *vs.* 32.45(14.15–94.38) KU/L, $p = 0.003$]. After adjustment for traditional cardiovascular risk factors, a high serum IgE level was an independent predictor for an increased risk of MVD (OR 1.003; 95% CI 1.001–1.004; $p = 0.041$). Receiver-operating characteristic curve analysis demonstrated that serum IgE levels improved the predictive capability of traditional risk factors for MVD (area under the curve with and without IgE: 0.734 and 0.713, respectively, $p < 0.001$). Meanwhile, there was a significant linear relationship between Gensini score and the serum IgE level quartiles (p for linear trend <0.001).

Conclusions: Increased total serum IgE levels are associated with MVD and contribute to discriminating CAD severity independently of traditional cardiovascular risk factors.

1. Introduction

Atherosclerosis is an inflammatory disease associated with multiple risk factors and a complex pathophysiology [1,2]. Among the various mechanisms involved in the development, growth, and rupture of atherosclerotic plaque, several lines of evidence suggest that an allergic type of inflammation plays a role in atherosclerosis-related diseases [3,4].

Immunoglobulin E (IgE) is a key component of a network of proteins implicated in signaling response to allergens/antigens and participates in atopic disease and systemic anaphylaxis [5]. This immunoglobulin is synthesized and released by B lymphocytes as a result of complex interactions between genes, cytokines, and environment [6]. Their biological activity is mainly dependent upon binding to specific Fc receptors present at the surface of mast cells (MCs), basophils, and monocytes [7]. Over the past decades, the interrelationships between allergy, IgE and atherosclerosis have gradually come to light. Evidence from animal models and in vitro experiments suggests that the interactions between IgE and MCs trigger the direct or indirect release of a variety of substances [4,5]. These substances not only critically contribute to the progression,

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erosion and rupture of atherosclerotic plaque but also are involved in the occurrence of subsequent thrombotic complications resulting from platelet activation and fibrinolytic system impairment [4,5,8,9]. Furthermore, IgE itself and the interactions with MCs are implicated in inducing coronary artery spasm independent of atheromatous disease, as well as promoting the development and growth of artery aneurysms [10–13]. At the same time, clinical studies indicate that the plaque destabilization is strongly associated with the total serum IgE concentrations. The serum IgE levels significantly increase in patients with coronary artery disease (CAD) when compared to unaffected subjects [14,15]; the highest IgE levels are detected in patients with acute myocardial infarction (AMI), followed by those with unstable and then those with stable angina pectoris [10]. Besides, an increase in total serum IgE levels was reported to be an independent prospective risk factor for future myocardial infarction [16]. However, the relationship between total serum IgE levels and the atherosclerotic plaques burden of coronary arteries in CAD patients remains unclear. Whether the serum IgE levels are associated with CAD severity and capable of predicting CAD was investigated in this study.

2. Materials and methods

2.1. Study population

Patients presented to Peking Union Medical College Hospital for coronary angiography between January 2013 and October 2015 were recruited consecutively into this study. Given the known association of total serum IgE with allergic diseases, parasites infection, cancer, and autoimmunity, we excluded patients with the following conditions to limit potential confounding factors: asthma, autoimmune diseases, allergic dermatitis, history of allergic diseases, parasites infection, malignancy, severe renal failure (estimated glomerular filtration rate <30 mL/min), chronic hepatic disease, rheumatic heart disease, valvular heart disease. Patients with coronary spasm, current infection, heart failure or shock were also excluded from the study. This study was approved by the ethics committee of Peking Union Medical College Hospital and conducted according to the principles described in the Declaration of Helsinki. Written informed consent was obtained from all study participants.

Subjects with <50% stenosis in coronary arteries were defined as non-CAD patients, while CAD was diagnosed according to the presence of more than 50% stenosis in at least 1 main coronary artery. We then classified the patients with CAD according to the number of diseased vessels into single-vessel disease (SVD) and multivessel disease (MVD) groups. At the same time, CAD patients were also sub-divided into 3 groups as follows: (1) stable angina pectoris (SAP); (2) unstable angina pectoris (UAP); (3) acute myocardial infarction (AMI). UAP was defined by the following criteria: prolonged (>20 min) angina pain at rest, new onset angina (Class II or III according to the Classification of the Canadian Cardiovascular Society), recent destabilization of previously stable angina with at least Canadian Cardiovascular Society Class III angina characteristics (crescendo angina), or post-myocardial infarction angina [17]. SAP was defined as angina that did not fulfill the above UA criteria [18]. Myocardial infarction was defined according to the third definition of myocardial infarction [19].

2.2. Coronary angiography and image interpretation

Coronary angiography was performed with an angiography unit (Integris H; Philips Medical Systems, Amsterdam, the Netherlands). Coronary artery stenosis was imaged from multiple projections. Two expert cardiologists who were blinded to the patients' clinical and laboratory data reviewed the coronary angiography and evaluated the coronary atherosclerotic lesion severity independently. The atherosclerosis severity was determined using the Gensini score (GSS), which is calculated by assigning a severity score to each coronary stenosis according to the degree of luminal narrowing and localization [20].

2.3. Patient information recording, sample collection and analysis

Patient information was recorded, including age, gender, height, weight, BMI, history of hypertension, history of diabetes, and smoking status (current smoker is the patients who have consumed tobacco in recent 3 months). Hypertension and diabetes were diagnosed according to the current guidelines [21,22]. All laboratory and clinical parameter data were obtained from a careful review of the patients' medical records at index admission. Blood for determining total serum levels of IgE was collected from the vein once patients were hospitalized and prior to coronary angiography. Human serum IgE levels were detected using an ImmunoCAP total IgE assay with Phadia 1000 Immunoassay Analyzer (Thermo Fisher Scientific Inc., Waltham, MA, USA) according to the manufacturer's instructions.

After an overnight fast for 12 h, peripheral venous blood was drawn from all the patients to determine the lipid profile (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides), creatinine, and high-sensitivity C reactive protein. These measurements were performed on an Architect C8000 by commercially available tests from Abbott (Abbott diagnostics, Santa Clara, CA, USA). All tests were measured under standardized conditions in an accredited local laboratory of the Peking Union Medical College Hospital.

2.4. Statistical analysis

The one-sample Kolmogorov-Smirnov test was used to determine the distribution normality of the data for the continuous variables. Normally distributed data were expressed as mean ± standard deviation, and data with skewed distributions were expressed as the median with inter-quartile ranges. Categorical variables were summarized as count and percentage. Continuous variables were compared with the use of the independent 2-tailed student's *t*-test or Mann-Whitney U test between two groups (the non-CAD *vs.* CAD groups and the SVD *vs.* MVD groups). Categorical variables were compared by chi-square test or Fisher exact test. Multivariate logistic regression was used to determine the independent predictors of CAD or MVD in a stepwise backward conditional manner, with entry and retention in the model set at a significance level of 0.05. We also evaluated improvements in the discrimination after adding serum IgE levels to a model consisting of traditional cardiovascular risk factors with an increased area under the curve (AUC) in receiver-operating characteristic analysis. Whether the serum IgE levels provided a better-fit model to discriminate MVD compared with known conventional risk factors was analyzed using the likelihood ratio $\chi 2$ test. Analysis of variance (ANOVA) trend tests were employed to assess the linear trends between GSS and the quartiles of serum IgE concentrations. A p value $\leq$ 0.05 was considered statistically significant. Statistical analysis was performed using SPSS Statistics software, version 20.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Baseline clinical characteristics

A total of 708 patients (452 men and 256 women; mean age