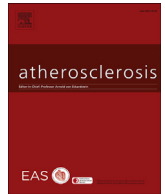




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Serum IgE levels in coronary artery disease

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ABSTRACT

The development and progression of atherosclerosis and its predisposition for unstable angina, myocardial infarction and stroke is associated with traditional risk factors such as family history, cigarette smoking, hypertension, dyslipidemia, diabetes mellitus, obesity, imbalance of the hemostatic/fibrinolytic system and sedentary lifestyle. However, much of the variability in atherosclerosis and its manifestations still remains unexplained. Nowadays, there is increasing evidence that immunologic mechanisms play a major role in etiology, prediction of coronary plaque instability and foreseeing severe reaction leading to an actual coronary event. Cells of the immune system such as macrophages, mast cells and T-lymphocytes are major components of human atheromatous plaque. These cells participate in a vicious immune cycle and activate each others via bidirectional stimuli. For example, mast cells can activate macrophages and may enhance T-cell activation. Inducible macrophage protein 1a may activate mast cells, while CD169+ macrophages activate CD8 T cells. T cells may mediate mast-cell activation and proliferation and regulate macrophage activity.

Mediators secreted by these cells, including histamine, neutral proteases, arachidonic acid products, platelet activating factor and a variety of cytokines and chemokines, can induce coronary artery spasm and atheromatous plaque erosion and rupture, culminating in the development of acute coronary syndromes.

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Immunoglobulin E (IgE) is an important regulator of allergic reactions because by binding to high and low affinity FcεRI and FcεRII receptors, situated on the mast and macrophage cell surface, can activate these cells to release their mediators. In addition to these cells, other inflammatory cells such as eosinophils, platelets, monocytes and dendritic cells also bear high and low affinity receptors on their surfaces [1–3]. Therefore, IgE's targets likely extend beyond mast cells to induce coronary events and to contribute to immunological procedures.

In this issue of *Atherosclerosis*, Guo et al. [4] measured total serum IgE concentrations in 708 consecutive patients admitted to coronary angiography laboratory, and assessed the severity of coronary artery disease by the number of diseased vessels showing ≥50% diameter stenosis and quantified by Gensini scores. They found that total serum IgE levels were significantly increased in patients with multi-vessel disease compared to those with single-vessel disease, were independent predictors for an increased risk of multi-vessel disease, and contributed to discriminating coronary

artery disease severity independently of traditional cardiovascular risk factors.

Several other studies have also shown that increased serum IgE concentrations are present during acute coronary syndromes and have emphasized the significance of measuring them in patients with coronary events as shown chronologically:

- 1 A cross sectional population study [5] that included 262 men and 315 women has shown a statistically significant positive correlation between increased IgE levels in men, but not in women. Previous myocardial infarction, stroke, and peripheral arterial disease were found irrespective of total cholesterol and LDL levels.
- 2 A study [6] concerning 156 patients with coronary heart disease, who were admitted to cardiological wards, showed that total IgE levels were significantly higher in patients with unstable angina and acute myocardial infarction compared to patients with stable angina and controls.
- 3 In a prospective [7] study of 621 patients followed for about nine years, a significant correlation between the increased IgE levels and the incidence of acute myocardial infarction in males was

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- found. When IgE levels were above 200 kU/L, the incidence of non-fatal myocardial infarction was even higher.
- 4 In another prospective clinical study [8], 55 patients with acute myocardial infarction, unstable angina and stable angina pectoris were compared with 15 healthy controls. IgE levels were serially measured on days 1, 3, 7, 21 after admission and 3 months later in the acute myocardial infarction and unstable angina groups and only once in the stable angina pectoris and healthy controls. In all groups, initial IgE levels were significantly higher than levels in the control group, and gradually decreased. Blood eosinophil count on admission was significantly higher in unstable angina than in the control group. It was concluded that the level of IgE significantly increased during the acute phase of acute coronary syndromes and gradually decreased, supporting the role of acute inflammatory response and mast cell involvement in plaque rupture.
 - 5 The incidence of complications (heart failure, recurrent angina, arrhythmia and coronary interventions) and in-hospital mortality were prospectively assessed in two study groups [9] consisting of 43 patients with preinfarction angina, within 24 h before the onset of acute myocardial infarction (preinfarction angina group), and 50 patients without preinfarction angina (sudden onset group). White blood cells and CRP were significantly lower in the preinfarction angina group than in the sudden onset group. Conversely, IgE and C4 were significantly higher in the preinfarction angina group than in the sudden onset group.
 - 6 Forty patients with stable angina pectoris, 40 patients with unstable angina pectoris, 40 patients with acute myocardial infarction and 40 post-CABG-surgery acute myocardial infarction patients were compared with 40 normal subjects [10]. An increased IgE but unchanged MMP-9, CPK, LDH were found in the stable angina group and unstable angina group, whereas IgE, MMP-9, CPK and LDH levels were all significantly increased in the acute myocardial infarction group. IgE, MMP-9, CPK and LDH levels in the P-CABG group were significantly reduced, compared with the acute myocardial infarction group, and were similar to those in normal subjects. Cholesterol, LDL, HDL and triglycerides were not significantly changed in all groups. It was suggested that serum total IgE can be an early marker of coronary artery disease and MMP-9 is a marker of acute myocardial infarction.
 - 7 Significant increase of thrombinogenesis and fibrinolysis markers was detected in a study of 80 patients with acute myocardial infarction [11]. In this study, a positive correlation between IgE concentration above 100 kU/L and markers of thrombinogenesis activation, lipid parameters and lipoprotein(a) levels, was found. A constant positive correlation between increments of IgE and markers of thrombin generation was observed. It was concluded that there is evidence of IgE participation in the atherothrombotic process.
 - 8 In another study [12] of 195 patients suffering from any form of ischemic heart disease, serum IgE levels were increased as compared to the control group of healthy individuals. IgE serum levels, on day 1, 7, 14, and 40 after acute myocardial infarction, did not revealed any significant differences. Males had significantly higher IgE than females.
 - 9 Finally, in a study concerning the hyper-IgE recurrent infection syndrome (Job's syndrome) [13], a disorder affecting the immune system and connective tissues caused by autosomal dominant STAT3 mutations and associated with coronary abnormalities including tortuosity, ectatic dilation and focal aneurysms, it was found that STA3 plays an integral role in human vascular remodeling and atherosclerosis.

Despite that IgE concentration has been found increased in coronary events, the important questions which arise and need an answer to which came first, the chicken or the egg, are: firstly, are elevated IgE levels indicative of their participation in the development of the coronary event or are increasing due to inflammatory reaction from tissue damage occurring during the event? Secondly: Do increased IgE levels precede or result from acute coronary event?

In a recent important study, it was found that circulating IgE levels in patients with atherosclerosis are associated with plaque instability, which precedes acute coronary events [14]. In this study, immunostained parallel frozen sections of human atherosclerotic lesions from shoulder regions of atheromatous plaque showed that IgE and its high-affinity receptor FcεR1 localized to macrophages in the shoulder regions and lipid cores, to smooth muscle cells in the fibrous cap, and to embryonic cells in the lumen and microvessels. It is known that shoulder sites of coronary plaques are susceptible to erosion or rupture, which means that IgEs, their receptors, and inflammatory cells invade this area before an actual initial coronary event. Indeed, infiltrates of activated mast cells were also found at the shoulder region of coronary atheromatous erosion or rupture in a ratio of 200:1 compared with normal adjacent endothelial segments. It is known that circulating blood contains only mast cell precursors and these precursors take several days to weeks to differentiate into morphologically identifiable mast cells filled with cytoplasmic secretory granules. Therefore, the mast cells must already have been present at the erosion or rupture sites before the episode in the above patients.

In the Helsinki Heart Study evaluating immunoglobulin levels in 270 participants, with initially healthy hyperlipidemic men who suffered myocardial infarction, the levels of IgE as well as of other immunoglobulin classes such as IgA, IgG were significantly higher before the event than the matched healthy controls [15]. The risk of myocardial infarction increased with the increase of immunoglobulin level and was independent of adjustment for confounding factors such as age, smoking, or blood pressure. The conclusion was that myocardial infarction was preceded by immunological processes involving antigen–antibody systems.

Therefore, the observed higher levels of immunoglobulin E in patients with cardiovascular diseases and their association with ischemic heart disease could serve as an early marker of atherogenesis and its consequences that could predict future coronary events.

Further studies are needed to corroborate this. The definite answer to the dilemma whether total IgEs are considered simple biomarkers or risk factors of ischemic heart disease would pave the way to investigations focused on immunotherapy or avoidance of allergenic foods for reducing serum IgEs in patients at risk of IHD [16].

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