Abstract

Background- Recently, mast cells have been found to participate in the inflammatory process of atherosclerosis. Mast cells can be activated by IgE-mediated mechanisms to release potent mediators which also affect coronary blood flow. The aim of this study was to determine serum IgE levels in patients with acute ischemic syndromes.

Methods- Serum samples were collected from 3 groups consisting of 30 patients with acute myocardial infarction (AMI), 30 patients with unstable angina pectoris and 30 subjects without any ischemic heart diseases, as a control group. The serum IgE levels were measured by sandwich ELISA technique.

Results- The mean serum IgE concentrations in AMI, unstable angina and control groups were 367.1, 286.2 and 136 IU/ml, respectively. There was a significant difference between the IgE levels in patients with AMI and those in the control group (p<0.01). Moreover, there was a significant association between IgE levels and acute ischemic syndromes in men as compared to women.

Conclusion- Elevated levels of serum IgE were observed in patients with ischemic heart diseases. These results suggested that IgE might play an important role in the immunopathogenesis of AMI and unstable angina or that it could only be a marker formed during pathological mechanisms (Iranian Heart Journal 2004; 5(1,2):20-25).

Key words: IgE, acute myocardial infarction, unstable angina, Rafsanjan.
Furthermore, *in vivo* administration of histamine and other mast cell-derived mediators causes significant cardiovascular effects.\(^9\)

Cardiovascular involvement in acute allergic events is a known phenomenon. A strong association is observed between day to day variation in pollen concentrations and the deaths due to cardiovascular disease.\(^10\) There are several reports of arrhythmia, myocardial ischemia and infarction during anaphylactic reactions. In these situations, cardiovascular alterations are thought to be generated by histamine or other products of mast cells.\(^11,12\) The possible role of IgE in cardiovascular disease has received little attention. A few reports indicate a potential link between elevated levels of IgE and coronary arterial disease. We conducted a study for the first time to measure serum IgE levels in Iranian patients with AMI and unstable angina pectoris.

**Materials and Methods**

A total of 60 patients (aged 40 to 65 years) with ischemic heart disease who were admitted to Ali-ibn-Abitaleb Hospital of Rafsanjan (a city located in Kerman province in the south-east of Iran) were enrolled in the study. The patients were then classified into 2 groups according to well-established criteria, as having AMI (19 men and 11 women) or unstable angina (19 men and 11 women). AMI was diagnosed by the presence of two of three criteria: 1-prolonged chest pain compatible with AMI, 2-typical ECG changes and 3-an increase in cardiac enzymes. Unstable angina patients were in class IIIB according to the Braunwald classification. Only patients who had no identified major risk factor for ischemic heart disease such as hyperlipidemia, hypertension, obesity, diabetes, smoking history, or positive familial background were enrolled into the study. Indeed, patients who had at least one of these risk factors were excluded from the study. Other exclusion criteria were malignancy, surgery, major trauma and inflammatory disease in previous months. Serum IgE levels were measured in patients with AMI between 2-3 weeks after admission. In patients with unstable angina, measurements were taken at admission. A third sex and age-matched group, comprising 30 subjects (19 men and 11 women) with no ischemic heart disease, was registered as a control group. Peripheral blood (2-4 mls) was collected from the subjects of the 3 groups, and the serum was separated and stored at \(-20^\circ\)C. Serum IgE levels were quantitated in duplicate by enzyme-linked immunosorbent assay (ELISA), using commercial kits (Radim, Italy). Serum IgE concentration was expressed as IU/ml. Differences in variables were analyzed using the Anova, Mann-Whitney U and Kruskal-Wallis tests as appropriate, and p values of less than 0.05 were considered significant.

**Results**

The mean concentrations of IgE were 367.1, 286.2 and 136 IU/ml for AMI, unstable angina and control groups, respectively (Fig. 1). Serum IgE levels of both AMI and unstable angina groups were found to be elevated as compared to those of the control group, although statistical analysis revealed only the AMI group had significantly higher levels of serum IgE than control individuals (p < 0.01). The concentration of IgE in serum did not significantly differ between the AMI and unstable angina groups. Moreover, no statistically significant difference was found between the serum IgE level of unstable angina and the control groups. Table 1 demonstrates the serum IgE levels in men and women. As demonstrated, there
was a more important association between IgE levels and ischemic heart disease in men as compared to women. Overall, in the three groups, men had higher levels of IgE than women. The mean concentration of serum IgE for men in AMI, unstable angina and control groups were 401.2, 288.4 and 148.3 IU/ml, respectively (P <0.05). Statistical analysis demonstrated that the concentration of serum IgE did not significantly differ between the women in AMI, unstable angina and control groups.

Table I: Comparison of serum IgE levels between AMI, unstable angina and control groups according to sex.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Sex</th>
<th>No</th>
<th>IgE Level (IU/ml)</th>
<th>P.Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>Male</td>
<td>19</td>
<td>401.2 ± 484.9 *</td>
<td>N.S</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>11</td>
<td>308.4 ± 430.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>30</td>
<td>367.1 ± 460.4</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>Male</td>
<td>19</td>
<td>288.4 ± 430.5 *</td>
<td>N.S</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>11</td>
<td>282 ± 458.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>30</td>
<td>286.2 ± 434.1</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>Male</td>
<td>19</td>
<td>148.3 ± 206 *</td>
<td>N.S</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>11</td>
<td>114.7 ± 89.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>30</td>
<td>136 ± 171.5</td>
<td></td>
</tr>
</tbody>
</table>

*Represents that the mean concentrations of serum IgE for men of three groups were statistically significant (p<0.05). N.S: means that the differences of serum IgE levels between men and women are not significant.

**Discussion**

The present study demonstrated that in Iranian patients with AMI and unstable angina pectoris, levels of serum IgE are significantly higher when compared to a control group. Similar results were obtained in other studies. This finding may provide valuable new insights into the pathophysiology of ischemic syndromes. The classic example of mast cell stimulation is their activation by IgE. In IgE-mediated degranulation, the relevant antigen (allergen) is bound by two or more of the IgE molecules bound to receptors with high affinity for IgE (FcεR) on the mast cell surface. This cross-linkage of cell-bound IgE with bridging of IgE receptors triggers mast cell degranulation. However, IgE-mediated release of histamine, leukotrienes, and other products can alter the local flow of blood.

Indeed, increased blood histamine levels were detected in some patients with acute myocardial infarction. Histamine constricts or dilates human coronary arteries, depending on the size of the vessel and its structural changes. PGD2 and leukotrienes are also powerful vasoconstrictors of human arteries.

Another mechanism suggested by an autopsy study in Finland showed up to a 50-fold increase in activated mast cells in human atheromas. IgE-mediated responses can also produce platelet activation or aggregation, stimulate the release of platelet activating factor and cause platelet-dependent smooth muscle hyperplasia. However, the formation of thrombus is the major factor in the genesis of acute ischemic syndrome. Mast cells can release proteases such as tryptase and chymase, which could trigger matrix degradation leading to destabilization and atheroma rupture, potentially triggering an acute coronary event. Taken together, these observations raise the possibility that...
the local activation of cardiac mast cells though the release of various mediators, might contribute to certain cardiovascular diseases.

It was also reported that when a lipid-rich diet was applied with allergens, experimental atherosclerosis was accelerated. Thus, it can be speculated that events mediated by circulating IgE have a role in the genesis of ischemia, as in AMI and unstable angina pectoris.

Furthermore, an association between blood eosinophilia and myocardial diseases has been demonstrated. It has been reported that the increase in eosinophil count is similar to the increases in levels of IgE. This is interesting, since eosinophils have specific IgE receptors. Eosinophils and their products might adversely affect the course of myocardial infarction. Eosinophil cationic protein, known for its cytotoxic properties, has been observed in increased concentrations in the serum of patients with AMI and angina pectoris. It should be noted that helper T-cells have been divided into two subsets based on cytokine profiles that they secrete upon antigen stimulation. Th1 cells secrete IL-2 and IFN-γ, while Th2 cells secrete IL-4, IL-5, IL-10 and IL-13. IL-4 and IL-13 stimulate B-cells to secrete IgE, and IL-5 induces the proliferation and differentiation of eosinophils. Moreover, mast cell-derived IL-4 in turn induces the differentiation of Th2 cells. As a result, it thus seems that Th2 cells are stimulated in patients with acute ischemic syndromes.

Our results demonstrated an association between serum IgE levels and ischemic heart disease in men, but not in women. Men in each of the three groups had higher levels of IgE than women. Similar results were obtained by Langer et al., although in that study higher levels of serum IgE in men were attributed to a higher frequency of cigarette smoking in men compared to women. However, in our investigation, any patient with a history of cigarette smoking history was excluded from the study. Thus, the underlying mechanism for this association between serum IgE levels and ischemic heart disease in men is unknown. It has been reported that an elevated serum IgE level is a strong independent prospective risk factor for the development of ischemic heart disease, so that serum IgE levels above 200 IU/L are associated with nearly seven times the risk of incidence of AMI, without any prior history of coronary events. Accordingly in some situations it seems unlikely that the levels of IgE are elevated after the coronary event, because in some studies, the measured serum IgE levels are exceptionally stable and the IgE level is not known to be affected by the use of medicines other than steroids. In other words, repeated IgE measurements show no fluctuation, and the levels measured are constantly elevated.

On the other hand, the results of some studies demonstrate that the serum level of IgE significantly increases during the acute phase of coronary syndromes and gradually decreases, supporting the notion that the early rise in serum IgE level should be a part of an increased humoral immune response against the protein released from the necrotic heart tissue. Accordingly, IgE may play a direct role in the pathogenesis of ischemic heart diseases, or it may only be a marker formed during pathological mechanisms. Moreover, it has been reported that a higher serum IgE concentration may act as a marker for favorable prognosis in patients with myocardial infarction. On account of these observations, an early determination of serum IgE level might help to detect patients at risk of sudden cardiac death during myocardial infarction. However, few studies have compared different factors affecting the prognosis and sensitivity and financial aspects of
different prognostic strategies. The results of our study encourage further studies to investigate the prognostic value of serum IgE levels in Iranian patients with ischemic heart diseases.

In summary, higher serum IgE concentrations were observed in Iranian patients with AMI and unstable angina pectoris as compared to those in the control group. The present results support the notion that IgE may be a marker formed during pathological mechanisms, or that inflammatory and immunopathological responses such as IgE and mast cells may play an important direct role in the pathogenesis of ischemic heart disease.

References


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