



CLINICAL MEDICINE

ELEVATED LEVELS OF PLASMA IMMUNOGLOBULIN E  
IN PATIENTS WITH CARDIAC SYNDROME X

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ABSTRACT

Cardiac syndrome X is a status described by the presence of angina pectoris, a positive response to exercise stress test with angiographically normal epicardial coronary arteries. The pathogenesis of cardiac syndrome X has previously ascribed to myocardial ischemia that may be caused by microvascular endothelial dysfunction and increased sensitivity to intracardiac pain. However, despite the extensive studies, the precise mechanisms in cardiac syndrome X remain unclear. More recently, the data has been suggested that chronic inflammation has been associated with cardiac syndrome X. The evidence for the hypothesis include that cardiac syndrome X is associated with elevation of several inflammatory biomarkers, suggesting a possible role for inflammation in its pathogenesis. Recently, enhanced levels of serum immunoglobulin E in patients with cardiovascular diseases have been generating more interest. The aim of the study was to establish the role of immunoglobulin E in the mechanism of cardiac syndrome X induction.

The study included eighty patients with cardiac syndrome X (30 male/50 female; mean age: 51.72±9.20 years) and 60 healthy age- and gender-matched individuals (21 male/39 female; mean age: 49.35±5.45 years). Every subject was interviewed concerning presence of allergy, concomitant acute/chronic diseases, tobacco abuse and other risk factors for coronary arterial disease. Plasma immunoglobulin E concentration measurements were carried out using ELISA technique.

Conducted studies revealed that patients with cardiac syndrome X were detected to have significantly higher plasma immunoglobulin E level in comparison with control group (115.64±34.60 IU/ml vs. 96.89±30.10 IU/ml, respectively;  $p=0.001$ ). In addition, the comparison of total immunoglobulin E concentrations between men and women did not reveal significant differences in both groups.

Thus, it can be concluded that the observed higher levels of immunoglobulin E in patients with cardiac syndrome X may serve as evidence that immunoglobulin E takes part in the pathogenesis of cardiac syndrome X, and, probably, it can be a marker, peculiarities of cardiac syndrome X course.

**KEYWORDS:** . cardiac syndrome X, immunoglobulin E, mast cell, inflammation.

INTRODUCTION

Cardiac syndrome X (CSX) is presented in patients as angina-like chest pain, a positive exercise stress test result and angiographically normal epicardial coronary arteries [Hurst T et al., 2006].

More than 40 years after the initial description

of the syndrome, the debate continues as to the mechanisms responsible for CSX, however, inflammation and microvascular dysfunction are two common, suggested pathogenic mechanisms [Li J et al., 2006]. Previously, mast cells have been implicated in the pathogenesis of coronary heart disease [Ma H, Kovanen P, 1995]. Mast cells are the only tissue cells expressing on their surface the high affinity receptor for immunoglobulin E (IgE) and synthesizing vasoactive factors [Sperr W et al., 1994]. Immunological activation of human

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heart tissue with anti-IgE induces the release of histamine [Graver L et al., 1986]. The concentration of histamine and the density of mast cells are increased in the arteries of cardiac patients [Patella V et al., 1998]. It was shown, that in vivo administration of histamine and other mast cell-derived mediators causes significant cardiovascular effects [Vigorito C et al., 1986].

In recent years, increased levels of serum IgE in patients with cardiovascular diseases have been generating more interest [Szczeklil A, 2000; Kubik L et al., 2002; Erdogan O et al., 2003a,b; Sinkiewicz W et al., 2008]. So far, it has not been disclosed whether the enhanced IgE concentration is a factor of the contribution of the immune mechanism to the development of the atherothrombotic process or whether it is indicative of the participation of antibodies in the inflammatory reaction to tissue damage [Sinkiewicz W et al., 2008]. The development of cardiovascular disease is associated with elevated levels of IgE, suggesting that IgE-mediated events play a role in the pathogenesis of these diseases [Criqui M et al., 1987; Erdogan O et al., 2003b]. Although, recent observations have revealed the role of inflammation in the pathogenesis of CSX, the mechanisms responsible for CSX pathogenesis are not well understood. Present study was conducted to establish the role of immunoglobulin E in the pathogenesis of cardiac syndrome X.

#### MATERIAL AND METHODS

The study included 80 patients (30 male and 50 female; mean age:  $51.72 \pm 9.2$  years) who had been diagnosed cardiac syndrome X and 60 healthy individuals (21 male and 39 female; mean age:  $49.35 \pm 5.54$  years) as control group. The entry criteria of CSX were recurrent typical angina chest pain at rest and on effort, a normal 12-lead electrocardiogram at rest, positive exercise ECG stress test response and a coronary angiogram. Patients with evidence of myocardial infarction, valvular heart disease, left and right ventricular dysfunction, hypertension, diabetes and a series of concomitant diseases were excluded from the study. Depending on individual case, non-cardiac causes of chest pain, for example during gastrointestinal and musculoskeletal diseases, were also investigated and ruled out as appropriate. Also, none of the control group patients had a previous history of

chest pain or acute/chronic diseases and none of them were taking cardiac or non-cardiac medication. All persons gave their informed consent prior to their inclusion in the study. The study protocol approved by the ethical guidelines of the Declaration of Helsinki (Br. Med. J. 1964; p.177) as reflected in the guidelines of the Medical Ethics Committee, Ministry of Health, Iran.

EDTA-anticoagulated peripheral blood samples were taken from each subject at rest on the same day that clinical data were recorded and the plasma was separated after a centrifugation of 3000 rpm for 10 min. Plasma IgE concentration measurement was carried out using commercially available IgE ELISA kits (Genesis Diagnostics, UK). The minimum detectable concentration of total IgE was 0.9 IU/ml.

Continuous variables are presented as mean  $\pm$  SD, and categorical data as numbers. Discrete variables were compared using the chi-square test. Comparison of continuous variables between two independent groups was done with the unpaired Student t-test. The analysis of the results was performed using SPSS 16.0 statistical software. A p-value of less than 0.05 was considered statistically significant.

#### RESULTS

The baseline characteristics of the study groups are presented in Table 1. There were no significant differences in age, sex, body mass index, systolic and diastolic blood pressure between two groups.

Figure 1 shows the comparison of the distribution of total IgE concentration in CSX patients with the control group. The plasma IgE levels were

Table 1.

Baseline characteristics of the study groups			
Indicators	Control (n=60)	Experimental (n=80)	p
Age (years)	49.35 $\pm$ 5.45	51.72 $\pm$ 9.2	0.078
Sex (male/female)	21/39	30/50	0.761
Body mass index (Kg/m <sup>2</sup> )	26.24 $\pm$ 3.39	26.54 $\pm$ 5.11	0.692
Systolic blood pressure (mmHg)	120.17 $\pm$ 7.01	114.75 $\pm$ 10.67	0.050
Diastolic blood pressure (mmHg)	75.75 $\pm$ 6.94	73.25 $\pm$ 7.76	0.267

higher in CSX patients than in control group ( $115.64 \pm 34.60$  vs.  $96.89 \pm 30.10$  IU/ml,  $p=0.001$ ) (Fig. 1).

The distribution of total IgE concentrations between men and women did not reveal significant differences in both CSX and control groups ( $p>0.05$ ) (Table 2).

TABLE 2.

Mean values and comparison of plasma IgE (IU/ml) concentrations between CSX and control groups according to sex.

	Controls	Cardiac syndrome x	p-value
male	$102.07 \pm 25.08$	$116.38 \pm 35.04$	0.296
female	$94.10 \pm 32.44$	$115.19 \pm 34.68$	0.882

## DISCUSSION

The present study demonstrated that levels of plasma IgE are significantly higher in patients with CSX while comparing with control group. IgE levels in healthy people are fairly stable; in clinical observations, no individual changes in the concentration were found throughout the period from 6 months to over 5 years. The higher values are observed in males than in females [Barbee R et al., 1981; Criqui M et al., 1990]. Burney's observations within the European Community Respiratory Health Survey, which analyzes the distribution of total and allergen-specific IgE antibodies in Europe, revealed diversified patterns of IgE distribution in different countries [Aas K, 1997].

In present study, plasma IgE concentrations turned out to be higher in CSX patients, significantly different from the control group. Despite the fact that there is no information in the literature regarding the association of IgE with CSX, similar differences in patients with ischemic heart disease as compared to the control group were observed by other authors [Kubik L et al., 2002; Erdogan O et al., 2003b].

The evaluation of the role that IgE plays in CSX is answering the question of whether enhanced IgE levels may be indicative of the immunoglobulin participation in the atherogenesis, or if the IgE concentration increasing in the course of CSX might be an indication of the inflammatory reaction to tissue damage. Recent findings have sug-

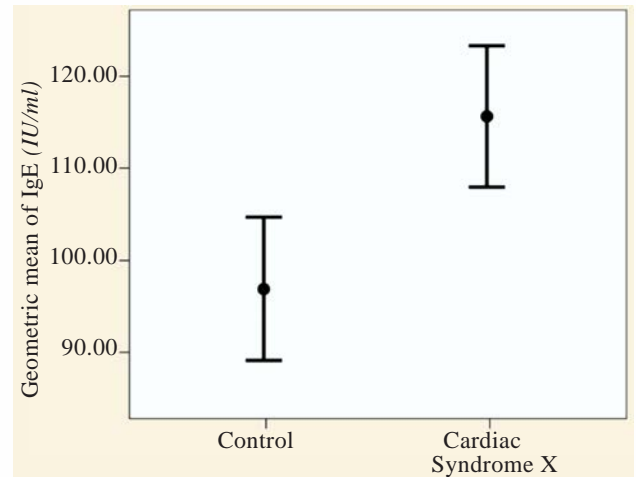


Figure 1. Comparison of plasma IgE levels between experimental and control groups

gested that chronic inflammation may contribute to endothelial dysfunction in CSX. There is evidence that those two indexes of systemic inflammation – C-reactive protein and interleukin-1 receptor antagonist are increased in patients with CSX compared with adequately chosen healthy control group, suggesting that low-grade inflammation may play a pathogenetic role in CSX patients [Lanza G et al., 2004]. Based on the observations of the authors, it can be speculated that IgE may play a double role.

In some researches higher values of serum IgE were observed in males than in females [Barbee R et al., 1981; Criqui M et al., 1987; Sinkiewicz W et al., 2008]. It is believed, that the increased serum IgE level in males is related to a higher incidence of cardiovascular diseases' occurrence [Criqui M et al., 1987]. Although women were reported to have lower IgE levels and a lower incidence of cardiovascular diseases, the prevalence of CSX is significantly higher in women compared to men [Kaski J, 2002]. In present study, there was no significant difference in IgE levels between male and female in CSX group. The study results are compliant with observations of M. Korkmaz and co-authors in which mean IgE concentrations were significantly higher in patients with ischemic heart disease, both in males and females [Korkmaz M et al., 1991].

The findings of present study may provide valuable new information referring to the pathogenesis of CSX. Cardiac syndrome x encompasses several possible mechanisms. Cardiac and non-cardiac

mechanisms have been proposed, among which endothelial dysfunction of the coronary microcirculation features prominently [Arraua-Espliguero R, Kaski J, 2006]. Numerous researchers have highlighted the potential importance of IgE which was reported to contribute to atherogenesis [Sinkiewicz W et al., 2008]. The classic example of mast cell stimulation is their activation and degranulation by IgE [Galli S, 1993]. IgE-mediated release of histamine, leukotrienes and other products can alter the local flow of blood [Galli S, 1993; Sperr W et al., 1994]. The local activation of cardiac mast cells despite the release of various mediators might potentiate the development of a series of cardiovascular diseases. Thus, increased blood histamine levels are associated with different types of ischemic heart diseases [Clemetson C, 1999; Gupta M et al., 2001; Zdravkovic V et al., 2011]. Histamine constricts or dilates human coronary arteries, depending on the size of the vessel and its structural changes [Clemetson C, 1999; Gupta M

et al., 2001]. IgE-mediated responses can also produce platelet activation or aggregation, stimulate the release of platelet activating factor and cause platelet-dependent smooth muscle hyperplasia [Gardiner C et al., 1999]. Thus, it can be speculated that events mediated by circulating IgE have a role in the genesis of ischemia, as in CSX.

The study results encourage further studies to investigate the prognostic value of IgE and also the potential therapeutic role of different antihistaminic medications and mast cells' roles in CSX disease.

Obtained results allow to come to a conclusion, according to which the shifts in IgE content in blood plasma of patients on the one hand testifies in favor of participation of mast cells in the pathogenesis of cardiac syndrome X, and on the other – the same concrete criterion of mast cells' functional state – the level of IgE can be reviewed as an additional, but at the same time an informative marker of diagnostics and course of present syndrome.

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