

Original Article

Evaluation of allergy and eosinophilia level in peripheral blood of patients with cardiovascular diseases

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Abstract

Background: Cardiovascular diseases are the most common cause of deaths in Iran and other developing countries. The risk factors for cardiovascular diseases are divided into two categories; the variable risk factors and the non-variable risk factors. Many recent studies evaluated the relationship between higher eosinophilia and allergy levels with the incidence, progress and severity of cardiovascular diseases, but the exact correlation between these two still remains unknown. The current study was designed to assess the relationship between allergic responses and eosinophilia amongst patients with cardiovascular diseases in Ilam province, in comparison with healthy individuals.

Materials and Methods: In this case-control study, we enrolled 59 cardiovascular patients and 55 healthy individuals without any history of allergy and parasitic infections. A questionnaire including questions about demographic data, family history of heart disease, history of diabetes, hyperlipidemia, physical activity, smoking, stress, dietary fat consumption, salt intake, allergies to certain substances, history of parasitic disease and history of hypertension was completed. The blood was taken from each participant and CBC and IgE titer were measured.

Results: There was a significant relationship for the variables such as the family history of cardiovascular disease ($P<0.001$), diabetes ($P<0.003$), hyperlipidemia ($P<0.0001$), high blood pressure ($P<0.0001$) and physical activity ($P<0.0001$) between the case and the control groups. The mean IgE titer in case group was 95.3 ± 71 and 62.44 ± 49 in control group. The mean eosinophilia level in peripheral blood was 3.95 ± 1.057 in case and 1.53 ± 0.57 in control group. The difference between the IgE and eosinophilia levels in the case and the control groups was statistically significant ($P<0.0001$).

Conclusion: Based on our results, it can be concluded the increase in levels of IgE and eosinophilia can be considered by cardiologists as a reliable diagnostic tool for predicting cardiovascular diseases.

Keywords: Allergy, eosinophilia, cardiovascular disease, antibody

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Introduction

Cardiovascular diseases (CVD) are the most common cause of deaths worldwide and also in developing countries, and nowadays it has been reported as the cause of death of about 20 to 30 percent of the population in Iran and around the

world [1-3]. These diseases impose high costs on the economy of countries, for example more than 450 billion dollars were spend by the United States in this regard [4, 5]. Although cardiovascular diseases and related –risk factors have the same pattern around the world, the average age of onset is higher in developed countries, because of the public health and clinical

efforts [6-8]. Most low and medium income countries (LIMIC) and even Iran, are in a state of "epidemiological transition", and the age onset is lower in developing countries. Notably, the average age of onset and the resulting mortality in Iran is lower than the world average in the recent 10 years, hence it has become a serious threat to public health [3, 9-13].

Risk factors of heart diseases include two categories of modifiable factors, such as hypertension, smoking, hyperlipidemia, sedentary lifestyle, diabetes, stress, pollution and drug therapy and unchangeable factors such as old age, male sex, the black race and family histories of cardiovascular diseases [13-15]. However, there is still a great deal of uncertainty about the major risk factors in patients with cardiovascular diseases [16].

Several studies reported the possible association between allergic reaction history and increased peripheral blood eosinophilia with cardiovascular diseases, [17-20]. This possible connection was firstly described by Kounis and Zefras in 1991. The symptoms of myocardial ischemia associated with allergic reactions is called "Kounis syndrome" or allergic myocardial infarction [21-23]. Recent studies suggest that coronary capillary contraction during an allergic reaction is induced by secretory inflammatory mediators of eosinophils and basophils, such as histamine and neutral protease [24, 25]. These inflammatory mediators are involved in inducing spasm and making atheromatous plaques or destroying coronary arteries, and they are the cause of acute coronary syndromes and have also been investigated as therapeutic targets [22, 26, 27]. In recent studies some cases with myocardial injury have been observed as clinical protests due to severe anaphylactic reactions, with regards to transfusion of amoxicillin (clavulanic acid). However, based on the cardiologic studies no obstruction or involvement of coronary artery have been found, but prick test for amoxicillin is positive and anaphylaxis can be the cause of myocardial injury, and its mechanism is similar to vasospasm induced by basophil mediators and mast cells [28-30].

In recent years, increased level of serum immunoglobulin-E (IgE) in cardiovascular diseases

has become an attractive issue of researches [31]. Studies show that the probability of acute coronary syndrome in atopic patients is higher than in normal people [29, 31]. Chriqui *et al.* in a population-based study found that the incidence of myocardial infarction and cardiovascular diseases in patients with high levels of IgE, significantly increased [32]. It still remains unclear whether increased levels of IgE can be considered as an indicator of the occurrence of cardiovascular problems, particularly coronary heart diseases in the future, or it can be introduced as a risk factor in ischemic heart disease, and perhaps as an indicator of inflammatory and injury responses of heart muscles due to antibodies [31]. However, the assessment of significant changes in the concentration of total serum IgE levels in ischemic heart problems and coronary capillary conflicts have been considered in comparison with normal IgE levels.

The new findings suggest that allergies and hyper eosinophilia syndrome (HES) can be a major risk factor for cardiovascular diseases, and many connections have been shown between allergy and increased level of peripheral blood eosinophilia, cardiac insufficiencies and acute cardiovascular problems in various studies [33-36]. Considering the possibility of a link between allergy and increased peripheral blood eosinophilia syndrome and a variety of cardiovascular diseases, the clarification of this issue can be effective in preventing heart diseases and applying treatment methods. This study is aimed at evaluating allergic responses in relation to the level of serum IgE antibody as well as peripheral blood eosinophil in cardiovascular patients in compared with healthy subjects.

Methods

This study was conducted in Ilam, Iran. The population of the study was 114, amongst which 59 of them were cardiac patients (29 men and 30 women), with a mean age of 37.12 ± 61.64 , who were in CCU of Mustafa Khomeini hospital in Khomeini city, Ilam, Iran, and 55 were healthy subjects (25 men and 30 women), with a mean age of 91.23 ± 38.51 with no history of allergy and parasitic disease. The calculation of sample size was performed using the software Epi-info and was under the Stat Calculation which use for case-control study. Based on 25% incidence of

cardiovascular disease in the society, with 99% confidence, 59 subjects were calculated for case group. This number was also chosen as a control group. It should be noted that the maximum consistency in demographic characteristics such as age, sex and other variables in choosing between the two groups were considered as well. In this study, all participants were interviewed based on a standardized questionnaire containing personal and demographic information, and lifestyle. Then, approximately 7 cc blood were taken in order to counting the number of peripheral blood eosinophil and frequency of IgE antibody titers. The counting of peripheral blood eosinophil number and frequency of IgE antibody titers were measured using complete blood counting (CBC) by Cell Counter - mind ray - BC 2800 and the ELISA kit IgE (Biomerio), respectively. Level of 5-1% of peripheral blood eosinophils was as normal and those higher than 5 percent were higher than normal and levels of IgE lower than IU/ml 188 were as normal and those higher than IU/ml 188 were as the above the normal range. In addition, no cross-reaction was observed with other antibody isotopes and all Missing data were reviewed.

Statistical analysis. All results were analyzed using SPSS version 15 and chi-square tests and independent t-test were performed in order to the examination of the prevalence of different categorical variables and survey of mean variables values,

respectively. The P value less than 0.05 (<0.05) is expressed as statistically significant.

Results

In this study, the titer of IgE antibody and the number of cells of peripheral blood eosinophils in cardiovascular patients were compared with control group. Also, the data analysis between the two groups included other variables, such as mean of age, mean of BMI, gender, education, occupation, family history of heart disease, history of diabetes, hyperlipidemia, physical activity, smoking, stress, dietary fat consumption, salt intake, allergies to certain substances, history of parasitic disease and history of hypertension. These were compared and analyzed, and data from the completed questionnaires are given in table 1.

Then, the mean of serum IgE titer and all the variables in the examined population were analyzed. It was found that the average level of IgE was significantly different in only four cases. A significant difference in the mean frequency of IgE titers between the two groups was seen in dietary fat intake (P=0.009), salt consumption (P=0.006), and allergies against certain substances (P= 0.006), as well as history of hypertension (P= 0.003). However, no significant differences were observed in term of other variables.

Additionally, the number of peripheral blood eosinophils in the studied population was analyzed. In this study, the only significant difference observed in this

Table 1: Evaluation of difference of variables between the control group and sample group.

Variables	Controls	Cases	(P value)
Mean of Age (year)	51.38±23.91	64.61±12.31	0.7
Sex			
male	45.4%	49.2%	0.071
female	54.6%	50.8%	
Body mass index (BMI)	21.9±2.31	24.23±3.97	0.033
Family history of heart disease (%)	5.5	28.8	0.001
History of diabetes (%)	1.8	18.6	0.003
History of Hyperlipidemia (%)	0	23.7	0.0001
History of Hypertensions (%)	5.5	69.5	0.003
Levels of physical activity (%)	7.3	39	0.0001
High intake of salt in food (%)	23.8	5.4	0.001
High stress levels (%)	9.1	40.7	0.001
High fat intake (%)	7.3	27.1	0.001
The mean IgE titers (IU/ml)	62.44 ±49.42	169.61±71.12	0.001
Average number of eosinophils (Per/mm ³)	1.53±0.573	3.95±1.057	0.001

population, was in the number of peripheral blood eosinophils in comparable physical activity ($P=0.037$), while in the two other variables, the difference between the two groups were so close. The difference between the two groups in terms of salt intake in the diet ($P=0.079$) and in terms of gender ($P=0.071$) were so close, with respect to the number of peripheral blood eosinophils.

The difference between mean concentration of IgE was statistically significant ($P=0.001$), as in patients with cardiovascular diseases, it was 12.71 ± 61.169 IU/ml, whereas it was 42.49 ± 44.62 IU/ml in the control group.

Also, a comparison between the average number of peripheral blood eosinophils in the two groups showed that it was statistically significant ($P=0.001$) (3.95 ± 1.057 per/mm³ in case group and 573.0 ± 53.1057 per/mm³ in the control group).

Discussion

In the present study, we showed that the prevalence of IgE titers and number of peripheral blood eosinophils in cardiovascular diseases compared with the control group was significantly increased. However, it is still unclear whether the increased levels of IgE, can be considered as a marker in the future for cardiovascular problems, especially coronary artery disease or can be introduced as a risk factor for ischemic heart. Also there is still obscure issue contribution as probable indicator in inflammatory and injury responses against heart muscle. The results showed that total serum IgE level in ischemic heart patients is significantly higher than the control group. Thus, increased density of serum IgE levels in cardiac ischemia patients can be as an indicator of allergic reactions in atherogenesis and myocardial ischemia. Moreover, our findings of increase in peripheral blood eosinophils suggests that the ecological reasons (vegetation variety in this region), genetics reasons, increased sensitivity to drugs, food, lifestyle agricultural products, the possibility of allergic reactions and increase in peripheral blood eosinophils may be involved in incidence, appearance and development of various cardiovascular diseases.

Along with evaluating of frequency of IgE titer and number of peripheral blood eosinophils,

other variables were also analyzed. Incidence of cardiovascular disease were also analyzed according to gender and sex influence on the incidence of CVD. In the current study 29 men, and 30 women were selected for the control group, the gender effect was not statistically important. Whereas, it was shown that gender is an important variable in CVD and it can be considered as specific risk factors for its occurrence, hence gender differences should be noticeable in the prevention and treatment [37]. Some literatures also show no significant difference between the severity of the stroke, symptoms, infraction value and the location between two genders [38].

Bazanov et al. in China, after the unification of variables such as age, sex, physical activity, residence, geographic diversity, smoking and diabetes among the case and control groups, showed that, increasing BMI is again as an important and independent risk factor for the occurrence of ischemic and hemorrhagic infarctions and it has been shown significant differences in increasing mortality due to cardiovascular diseases in Chinese citizens between the two groups [39] and it was consistent with our results.

There was also a significant link between the occurrence of cardiovascular diseases and family history of heart diseases in case and control groups, which was also observed in Paskvarla study in Italy [40].

Another finding of this study was a significant correlation between the occurrences of cardiovascular diseases based on history of diabetes in studied groups. This finding is similar to other studies such as the study of Howit et al. in Norway and Gomes et al in Spain [41, 42]. In the case of diabetes, the possibility of incidence and risk of development coronary artery diseases is 2-4 times higher, because it seems that in spite of hypertension, hyperlipidemia, obesity, endothelial damage and reduced function of the coagulation factors in diabetes mellitus type II, it has destroyed beneficial and protective hormones that can prevent coronary heart disease.

There was no significant association in this study regarding the occurrence of cardiovascular diseases and history of hyperlipidemia in the case and control groups. The study of Macce Duaie et al, in Greece showed a significant difference in term of total

cholesterol, LDL and lipoprotein lipase (α) among children with family history of CVD and CHD and the control group. They were aimed at evaluating the relation of CVD with history of hyperlipidemia, lipid profiles in children with positive family history of CVD and CHD incidence, and hyperlipidemia compared with healthy controls to determine risk factors for cardiovascular diseases [43].

In this study, the relationship between, blood pressure, and high input edible salt with a significant risk of incident CVD is significantly comparable and show that the increase in blood pressure can cause atherosclerosis and can be considered as a major risk factors for cardiovascular disease as it causes the 62% of heart attacks and 49% of acute coronary diseases. The studies Wang et al. in China, and Hue et al, demonstrated that there was a significant association between the occurrence of cardiovascular diseases, hypertension, and high input edible salt, which was partly in line with our findings [44, 45].

Notably, we found that there was an inverse relationship between physical activity and all causes of death due to CVD and CAD, which can be reinforced by study of Haynl et al. [46].

Based on this study, mental stress as one of the variables associated with CVD incidence is statistically significant as well. It is an important risk factor in the development and incidence of CVD which can cause disorder in endothelial function, myocardial ischemia, thrombosis and malignant cardiac arrhythmias. It was similar to studies of Merez et al. [47] and Vale [48].

Others found a significant relationship between the incidence of cardiovascular diseases and a history of allergies to specific substances. Kounis et al, investigated the relationship between allergies and cardiovascular diseases in term of coronary artery spasm induced by histamine and allergic angina in Greece. They reported that histamine is the main amine release in allergic reactions and can cause coronary artery spasm and produce clinical protests as an angina pectoris which is consistent with our results [21].

Interestingly, a significant relationship between the frequency of the IgE titers and number of peripheral blood eosinophils was shown based on studied variables in the case and control groups in

which there is a significant differences among the mean serum IgE titers and fat consumption in the diet, salt intake, hypertension, history of allergy to specific. To our knowledge, until now, no study reported the relationship between these variables and the mean serum IgE. Although, the exact reason underlying this association is still unknown, it seems that the allergies to certain substances may increase IgE levels in the case group.

Noticeably, it was found that about 66.7% of people whose eosinophils count are higher than normal ones, are immobility, while only 3.21% of those with normal eosinophil are low motion and this difference is meaningful. Accordingly, it seems likely that physical inactivity and immobility lifestyle are more probable among subjects with high number of eosinophil, while the number of normal eosinophils is high in most people with physical movement and exercise. We would like to stress that we reported possible association between immobility lifestyle and lack of physical activity and increasing the risk of peripheral blood eosinophilia for the first time. Also, we reported for the first time that the increased salt intake was observed among individuals with high eosinophils and subjects with high eosinophils have used 50% salt, whereas those with normal eosinophil have used only 15.7 % salt in their food. Collectively, it is possible that increasing consumption of salt in the diet can lead to peripheral blood eosinophilia.

Conclusion

We showed that the difference between IgE titers and number of peripheral blood eosinophils between the patient and control groups is significant. Also, it appears that the allergic reactions and increase in peripheral blood eosinophils contributes to high susceptibility to cardiovascular diseases. Hence, high levels of IgE antibodies and eosinophilia can be considered as an indicator in the development and the progression of various types of cardiovascular diseases. However, further studies are needed to establish efficacy of our findings .

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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