SERUM INTERCELLULAR ADHESION MOLECULE AS A DIAGNOSTIC BIOMARKER OF CORONARY ATHEROSCLEROSIS

Pakistan Armed Forces Medical Journal

June 30, 2016 Thursday

Section: No. 3

Length: 2938 words

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Body

ABSTRACT

Objective: To compare serum concentration of intracellular adhesion molecules i.e., ICAM in patients with coronary atherosclerosis as compared to controls.

Study Design: Case control study.

Place and Duration of Study: Armed Forces Institute of Pathology (AFIP) from January 2014 to June 2014.

Material and Methods: This study was conducted as a case-control study. A total of 110 patients undergoing coronary angiography were included, 55(50%) Patients were those who demonstrated at least one coronary vessel with > 50% stenosis on angiography. Whereas 55 (50%) individuals who demonstrated less than 20% coronary vessel stenosis on angiography were considered normal and were included in the control group. Serum ICAM was measured in both groups.

Results: Serum ICAM was found to be raised in 52(9401%) patients of the case group while it was raised in only 3(5.4%) patients of the control group. This increase was found to be statistically significant. Also the serum ICAM values were found to rise significantly with increasing vessel involvement.

Conclusion: Increasing concentrations of serum ICAM can be used as a biomarker of coronary atherosclerosis alleviating the need to employ invasive tests like coronary angiography to confirm the diagnosis.

Keywords: Atherosclerosis, Coronary angiography, Intracellular adhesion molecules.

INTRODUCTION

Ischemic Heart Disease (IHD) is a generic description of a group related cardiac events resulting from hypoperfusion of the myocardium. This hypoperfusion is a result of imbalance between oxygen delivery and myocardial metabolic demand. The resultant symptom complex of IHD is to a lesser extent triggered by increased myocardial metabolic demand and attributed in majority of cases to reduction of coronary blood flow resulting from atherosclerotic process of coronary arteries leading to their obstruction. Due to this analogy IHD is also frequently referred to as coronary artery disease4.

In spite of the monumental advances in IHD management over the last few decades, it still remains the leading cause of death. The symptomatology of IHD is a direct representative of coronary hypoperfusion. The understanding of the complex mechanics of evolution of plaque, its progression, the factors involved in the

progression of plaque at molecular level is of prime importance in understanding the disease so as to discover newer methods of detection of the disease in its earlier stages5.

The goal of modern medicine is to detect this disease in its initial stages to prevent its natural course. Focus has now shifted from radiological diagnosis to a molecular one, as imaging provides evidence of the disease only when it is fairly advanced. Research into molecular level showing tell tale signs of coronary atherosclerosis with the help of adhesion molecules may represent a new frontier in the diagnosis and hence management and eventually prevention of such a prevalent disease6.

Cellular adhesion molecules like iutracellular adhesion molecule (ICAM) and Vascular cell adhesion molecules-1 (VCAM-1) can be considered potential markers of vulnerability because such molecules are activated by inflammatory cytokines and chemokines and then released by the endothelium. At present these adhesion molecules are the sole available markers for assessing endothelial activation and vascular inflammation. Also ICAM levels showed a positive correlation with atherosclerosis disease burden. ICAM is a member of the immunoglobulin superfamily, i.e. the superfamily of proteins including antibodies and T-cell receptors. ICAM is known for its role in stabilizing cell-cell interactions and facilitating leukocyte endothelial transmigration7.

This study was done to compare serum concentration of adhesion molecules i.e ICAM in patients with coronary atherosclerosis as compared to controls.

MATERIAL AND METHODS

After approval by hospital ethical committee the research was conducted as a "Case Control Study" at Armed Forces Institute of Pathology (AFIP) over a period of 6 months from January 2014 to June 2014. A sample size of 110 patients (55 patients in each group) was calculated by using WHO sample size calculator. Sampling technique was "non-probability consecutive sampling".The patients were purpose divided into two groups: Case and Control. Cases consisted of CAD patients with at least 1 coronary vessel with > 50% stenosis. Controls consisted of normal individuals who demonstrated less than 20% coronary vessel stenosis (matched with respect to age and sex with cases). Patients of myocardial infarction, unstable angina, and with a history of acute/chronic infection were excluded.

All patients fulfilling the inclusion criteria were elaborately apprised about the study to obtain their informed consent. One hundred and ten patients undergoing coronary angiography and fulfilling the inclusion criteria were selected. Medical history and physical examination was carried out before angiography at AFIC Rawalpindi. Angiography was performed by consultant cardiologists. Laboratory investigations of all patients were performed at AFIP. Expenditure was borne by AFIP. Ten ml of blood sample was taken after an overnight fast before angiography by veni-punture into plane tube without the anti coagulant. The serum was separated by centrifuging at 3000 g and stored at -800C until biochemical analysis. Serum ICAM was performed by using fluorescent linked immuno assay kit. All the data was entered in a specially designed proforma attached as annexure A.

All data was analyzed using SPSS (version 13.0). Frequency and percentage was calculated for gender. Mean SD was calculated for quantitative variables like age, and serum ICAM levels. Independent sample T-test with Levenes correction was be applied to compare serum ICAM levels between cases and controls and also the effect on serum ICAM levels with increasing number of vessel involvement. A p-value less than 0.05 was taken as significant.

RESULTS

Out of the 110 patients there were 88 (80%) males (44 in each group) and 22 (20%) females (11 in each group). The age of patients varied from 38 to 73 years. Mean for age in the case group was 57.1 yrs with standard deviation 9.84, and in the control group mean age was 57.2 and standard deviation 10.26.

In the case group serum ICAM (normal range: 583.4 86.6 ng/ml) was found to be raised in 52 (94.1%) out of 55 patients (1593.2 85.3 ng/ml). Mean serum ICAM levels were 1178.2 + 186.3 in single vessel, 2075.7 + 85.4 in two vessel and 2218.2 + 167.8 in three vessel disease patients of the case group (p valueless than 0.008).

In the control group it was found to be raised in 3 (5.4%) individuals, mean 1176 + 32.4 (p value less than 0.001). The overall outcome variable in this study was subclinical atherosclerosis (confirmed by coronary angiography) designed to reflect increasing levels of ICAM in the individuals' serum.

DISCUSSION

Coronary artery disease (CAD) is a major health issue in the world. The incidence of CAD among the population of Southern Pakistan is 6.1%1. CAD is characterized by a chronic inflammatory disease of the arterial wall leading eventually to atherosclerosis. Multiple pro inflammatory cytokines are involved in the pathogenesis of CAD2. Inflammation is the main event in the pathogenesis of atherosclerotic plaque formation and progression and inflammatory markers could be useful for atherosclerosis risk prediction and stratification3.

Serum ICAM levels were found to be significantly raised in patients having coronary artery disease as compared to normal individuals, p value less than 0.001 (table-1). In cases 31(56.3%) patients had single vessel, 14 (25.4%) had two vessel and 10 (18.1%) had three vessel disease. Serum ICAM levels were seen to rise significantly with increasing number of coronary vessels affected with p value less than 0.008 (table-2).

The preliminary step in formation of atherosclerotic patch is leukocyte adhesion to the endothelial cell of the vessel wall followed by and transendothelial migration which leads to leucocyte aggregation. The above mentioned process is in part mediated by cellular adhesion molecules (CAMs), which attach to the endothelial cell membrane in response to activation by various inflammatory cytokines, like interleukin-1, tumor necrosis factor, and interferon2. Pathological examination has shown a many fold increase of CAM expression in atherosclerotic plaque which is backed by clinical data, which reveals the role of adhesion molecule in coronary artery disease in terms of a promoter and a possible marker for this potentially reversible phenomenon. The debate has originated for using ICAM-1 and sVCAM as biomarkers of coronary atherosclerosis, but also as a replacement of invasive procedures like coronary angiography8.

Table-1: Comparison of intercellular adhesion molecules between cases and controls.

Parameter	Mean ICAM (ng/ml)	SD	p-value
Cases	1593.2	85.3	
Controls	576	52.4	less than 0.001

Table-2: Comparison of vessel involvement with intercellular adhesion molecules levels.

Parameter	Single vessel disease		Two vessel disease		Three vessel disease		p-value
Serum ICAM (ng/ml) (Mean + SD)	1178.2	186.3	2075.7	85.4	2218.2	167.8	less than 0.008

Coronary atherosclerosis causes release of inflammatory cytokines which in turn generate increased expression of CAMS like soluble ICAM-1 and SVCAM. The mentioned cellular adhesion molecules play a crucial role in the migration of leucocytes from the blood to the arterial intima (transendothelial route). Beginning as early as 6 hours after an acute event of coronary blockage, increasing titres of circulating serum adhesion molecules i.e. ICAM-1, SVCAM, and soluble endothelial selectin (E-selection) can be detected and may be raised up to six months after the initial ischaemic event9.

The observations about role of adhesion molecules has also been verified indirectly by Cokerill et al,10 who demonstrated in cultured endothelial cells that high density lipoprotein can inhibit cytokine-induced expression of endothelial VCAM, ICAM, and E-selectin. Further to augment this statement a fall in serum levels of circulating adhesion molecule levels was seen when lipid apheresis was achieved in patients with familial hypercholesterolemia. Similar inferences were drawn by Zhang et al. who showed that lipid lowering diets and drugs decreased the levels of circulating sICAM-1 and sVCAM9.

Gross et al in a prospective study of 2738 individuals found a significant association between serum ICAM concentration and presence of both coronary artery calcification progression and carotid artery stenosis (precursor

of atherosclerosis). However no significant association was found on interaction between serum ICAM and C-reactive protein (CRP) on coronary artery calcification progression or carotid artery stenosis. This study was part of the Young Adult Longitudinal Study of Antioxidants (YALTA), an ancillary study to ***Coronary Artery Risk Development in Young Adults*** (CARDIA)11.

Rhode et al in randomized, double-blind cross sectional study, reviewed 948 males with no previous history of myocardial infarction but having positive history of factors contributiong to coronary disease i.e. smoking, hypertension, alcohol consumption and raised serum triglycerides. Serum ICAM was found to be significantly raised in individuals with the above mentioned risk factors all of which are positively related to development of coronary atherosclerosis. Apart from the risk factors ICAM-1 also had a positive correlation with fibrinogen, tissue-type plasminogen activator antigen, and total homocysteine which are hallmarks of chronic inflammation12.

A cross sectional study conducted by Idrus in 146 patients found that both serum ICAM and serum VCAM levels were significantly raised in patients of coronary heart disease. Furthermore serum ICAM and serum VCAM levels were significantly higher in acute cases as compared to chronic heart disease patients. The author concluded that ICAM levels can be used as predictor of an acute coronary event13.

Sokei et al in a cross sectional study inferred that serum SICAM concentration (ng/ml) on admission was higher in patients with acute myocardial infarction, unstable angina and stable angina. The authors have suggested that with these findings cutoff values can be determined to diagnose acute coronary event, decide about interventional procedures and even to stop medication on reversal of levels of circulating adhesion molecules14.

Jin et al in a cross sectional study employed 296 patients, deduced that serum levels of soluble intercellular adhesion molecule are raised in cases of coronary atherosclerosis and diabetes mellitus15.

Hung et al followed 189 patients over 28 months in which patients in various stages of coronary artery disease were followed and serum levels of soluble intercellular adhesion molecule were highest in cases of acute coronary event and lowest but still raised in cases of chronic coronary atherosclerosis. Serum levels of soluble intercellular adhesion molecule were also used by the authors as predictors of future acute coronary events in high risk cases16.

The most important aspect of SCAMs seems to be the ability to predict future coronary events in terms of high risk patients and also to determine the need of invasive coronary procedures. With fine tuning of the results high risk cases and those with strong family history can undergo invasive test provided they have raised serum ICAM.

CONCLUSION

Increasing concentrations of serum ICAM can be used as a biomarker of coronary atherosclerosis alleviating the need to employ invasive tests like coronary angiography to confirm the diagnosis.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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Classification

Language: ENGLISH

Publication-Type: Magazine

Subject: CARDIOVASCULAR DISEASE (93%); DIAGNOSTIC IMAGING (91%); ANGIOGRAPHY (91%); HEART DISEASE (90%); CASE STUDIES (90%); DISEASES & DISORDERS (89%); MEDICAL RESEARCH (89%); BIOCHEMISTRY (89%); PATHOLOGY (77%); RESEARCH REPORTS (73%); DISEASE MARKERS (66%)

Industry: DIAGNOSTIC IMAGING (91%); PATHOLOGY (77%)

Geographic: Pakistan

Load-Date: July 19, 2016