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Association of Inflammatory Mediators with Coronary Artery Disease in Diabetic Patients

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ABSTRACT

Background and Objectives: Coronary artery disease (CAD) is regarded as the leading cause of morbidity and mortality around the world. Diabetes mellitus (DM) is associated with the development of CAD and increased risk of morbidity and mortality. The goal of this study was to assess the association of tumor necrosis factorα (TNF-α) and high sensitivity C-reactive protein (hsCRP) with CAD severity in diabetic patients.

Materials & Methods: The cross-sectional protocol of this research was conducted on the referrals (n=81) of Chamran and Alzahra hospitals (Isfahan, Iran) in 2012. The severity of CAD was determined using angiographic findings and Gensini scoring system. TNF-α and hsCRP were measured in addition to some routine parameters. For statistical analysis, Chi-square test was used.

Results: Of the patients, 57 were male (70.3%) and 24 (29.6%) were female with a mean age of 54.2 years. In addition, a significant relationship was found out between the severity of CAD and level of hsCRP and TNFα ($p<0.05$-0.01).

Conclusion: Markers of inflammatory mediators like hsCRP and TNFα are strongly associated with CAD in diabetic patients that have clinically high prognostic value.

1. Introduction

Coronary artery disease (CAD) is regarded as the leading cause of morbidity and mortality around the world. A recent report on the Global Burden of Disease, which suggests disability-adjusted life years (calculated as the sum of years of life lost and years lived with disability) as a new measurement of CAD burden, indicates that the latter is accounted for the largest proportion of disabilities worldwide in 2010, explaining 5% of the total number of such conditions (1, 2). CAD is itself known as a complex chronic inflammatory disease, characterized by remodeling and narrowing of the coronary arteries supplying oxygen to the heart. It can have various clinical manifestations, including stable angina, acute coronary syndrome, and sudden cardiac death (2). CAD has a complex etiopathogenic and a multifactorial origin associated to environmental factors, such as diet, smoking, and physical activity, and background genetic factors that modulate its risk both individually and through interaction (3). Pathophysiologic mechanisms underlying the epidemiologic studies have been proposed and are under investigation. According to cohort studies, it has been found out that risk of cardiovascular accidents including myocardial infarction and CAD is correlated well with increased serum levels of inflammatory cytokines such as interleukin-6, tumor necrosis factor-α (TNF-α), adhesion molecules, and acute-phase proteins such as C-reactive protein (CRP) and fibrinogen. However, risk prediction based on these markers may be mainly secondary to major modifiable environmental, behavioral, and clinical risk factors like oxidative stress and inflammation (4).

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Diabetes mellitus (DM) is classified within the metabolic syndrome terminology and is a debilitating condition and as a cardiovascular risk factor. DM is associated with the development of CAD and increased risk of morbidity and mortality. The results of previous studies have shown that the prevalence of coronary heart disease (CHD) was significantly higher in diabetic subjects. Diabetes itself is a chronic, complex, and progressive illness that requires persistent medical care to prevent major cardiovascular complications (5, 6). The goal of this study was to assess the association of TNF-α and C-reactive protein with coronary artery disease in diabetic patients.

2. Materials and Methods

The protocols of this study were according to the Declaration of Helsinki for clinical studies and those of Isfahan Univ. Med. Sci. (Isfahan, Iran). This study was performed on 81 patients diagnosed with stable CAD and DM who had been hospitalized in the Alzahra and Chamran hospitals during the years 2011-12. Elective coronary angiography following a report of chest discomfort and stenosis that obstructed at least one main coronary lumen by ≥ 45% and with a prior history of myocardial infarction were done on patients. Criteria for exclusion from the study were those patients with unstable anginal pectoris, acute myocardial infarction, congenital heart disease, and severe renal or hepatic disease.

2.1. Biochemical analysis

Blood samples were taken after a minimum of 12-hour overnight fasting, collected in EDTA-containing tubes, and centrifuged at 3000 rpm for 20 minutes at 4°C. The plasma samples were stored at -70°C until analysis. Fasting levels of glucose, high-density lipoprotein (HDL)-cholesterol, albumin, creatinine, and blood urea nitrogen (BUN) were measured using an autoanalyzer. Low-density lipoprotein (LDL)-cholesterol was calculated using the Friedewald formula. Plasma TNF-α and hsCRP were determined using enzyme linked immunosorbent assay kits (R&D Systems Inc., USA) according to the manufacturer's instructions and were read by an ELISA reader (Biotek, USA).

Severity of CAD in patients with regard to coronary involvement in angiography was categorized into 3 levels, i.e. mild (< 10), moderate (10 -50), and severe (>50) basedon the Gensini score. The relationship between the hsCRP or TNF-α levels and the severity of CAD was analyzed using Chi-square test. The collected data were analyzed using the SPSS statistical software (version 17). A p value less than 0.05 was considered as statistically significant.

3. Results

The general characteristics of the patients are presented in Table 1. Of these patients, 57 were male and 24 were female with a mean age of 54.2 years. The results of the relationship between the hsCRP or TNF-α and severity of CAD have been presented in Table 2.

Table 1: Characteristics of patients

Age (years)	54.2 ± 1.7	Albumin (g/dl)	5.3 ± 0.4
Weight (Kg)	74.6 ± 1.9	ALP (IU/l)	181.3 ± 14.5
BMI (kg/m^2)	23.8 ± 0.8	LDH (IU/l)	193.4 ± 12.4
SBP (mmHg)	129.2 ± 1.2	Blood urea nitrogen(mg/dl)	17.2 ± 1.8
DBP (mmHg)	97.8 ± 0.9	Uric acid (mg/dl)	5.7 ± 0.5
Pulse (beats/min)	73.1 ± 1.8	Plasma creatinine (mg/dl)	1.8 ± 0.11
White blood cells ($x10^3/\mu l$)	7.4 ± 0.7	Total protein (g/dl)	7.4 ± 0.5
Red blood cells ($x10^6/\mu l$)	4.4 ± 0.1	Platelets ($x10^4/\mu l$)	21.5 ± 2.5
Plasma glucose (mg/dl)	146.7 ± 3.8	AST (IU/l)	19.7 ± 1.4
Hematocrit (%)	43.7 ± 0.9	ALT (IU/l)	25.1 ± 2.8
Hemoglobin (g/dl)	13.9 ± 0.17		

BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; Values are expressed as means ± S.E.M

Table 2: Frequency of patients with regard to CAD severity and plasma hsCRP or TNF-α

	Mild	Moderate	Severe	p value
hsCRP				
<1 mg/l	12	6	0	<0.05
1-3 mg/l	15	5	9	<0.01
>3 mg/l	1	18	15	<0.01
TNF-α				
	17 (<1 pg/ml)	31 (1-1.5 pg/ml)	33 (>1.5 pg/ml)	<0.01

4. Discussion

Coronary artery disease or sometimes known as atherosclerotic heart disease is as a result of the accumulation of atheromatous plaques within the walls of the myocardial coronary arteries. Although the symptoms and signs of CAD are noted in the advanced state of disease, most individuals with CAD show no evidence of disease for decades as the disease progresses before the onset of symptoms and often a sudden heart attack. After progression, some of these plaques may rupture and in parallel with activation of the blood clotting system limit blood flow to the heart muscle. CAD has been strongly correlated with smoking, diabetes, and hypertension. Diabetes is significantly associated with an increased risk of coronary artery disease. Screening for CAD usually includes evaluating high-density and low-density lipoprotein (LDL) (cholesterol) levels and triglyceride levels. Despite these markers, most of the alternative risk factors including homocysteine, inflammatory markers like C-reactive protein and TNF-α, coronary calcium are under intense investigation in addition to the conventional risk factors (7-11). The results of our study revealed a significant and strong relationship between the severity of CAD and plasma level of hsCRP and TNF-α. A similar relationship for hsCRP has also recently been reported by other researchers in non-diabetic condition (12, 13) that is somewhat consistent with the results of our study. In addition, a study by Masood et al in 2011 has also shown such a positive relationship (14). Meanwhile, this association with CAD has also been reported for TNF-α by Gostman et al in 2008 (15). The number of patients in these studies have been nearly similar to our study. A novelty of our study is that we have shown such a correlation in DM patients. In contrast to our study, a research by Ulucay et al in 2007 has shown that there is no relationship between hsCRP level and the presence and severity of CAD in patients with stable angina (16). This may be attributed to their small sample size. One of the limitations of our work was its small sample size that make our conclusion somewhat inconclusive. A similar study with a larger sample size is strongly recommended in future works.

Taken together, this study shows that markers of inflammatory mediators like hsCRP and TNF-α are strongly associated with CAD in diabetic patients that have clinically high prognostic value.

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