Turkish Journal of Endocrinology and Metabolism, (2006) 2 : 35-38 **ORIGINAL ARTICLE**

hs-CRP for Cardiovascular Risk in Diabetes: Problems in Daily Practice

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Serum levels of high-sensitivity C-reactive protein (hs-CRP) have been found to be a strong predictor for increased cardiovascular disease risk associated with type 2 diabetes independent of traditional risk factors. However, it is well known that hs-CRP level is influenced by various factors. In this study, we evaluated the non-metabolic factors affecting hs-CRP levels and their frequency, and we studied whether measuring hs-CRP has a clinical significance as a predictor for prognosis, in patients with type 2 diabetes.

Ninety-one consecutive patients (56 female, 35 male, mean (±SD) age: 53.7±10.2 years) with type 2 diabetes mellitus admitted to the Diabetes Outpatient Clinic of Istanbul Goztepe Training and Research Hospital were enrolled in this study. Medical history, physical examination, and laboratory findings of these subjects were evaluated in terms of the factors influencing hs-CRP level.

16.4% of patients had at least one of the non-metabolic factors increasing hs-CRP levels. Frequencies for smoking, hormone replacement therapy, acute infections and chronic infections were 14.2%, 3.2%, 7.6% and 4.3%, respectively.

In the present study, at least one of the non-metabolic factors capable of increasing hs-CRP levels was found in one of every six patients with type 2 diabetes, suggesting a limited use of hs-CRP for predicting cardiovascular risk.

Keywords: Diabetes mellitus, hs-CRP, cardiovascular risk factors

Introduction

Atherosclerotic cardiovascular diseases cause significant morbidity and mortality in patients with diabetes mellitus (1). Following the establishment of the significant role played by inflammatory mechanisms in the pathogenesis and complications of atherosclerosis, studies were conducted on inflammation indicator plasma molecules as potential predictors of cardiovascular risk (2-4). Large-scale trials performed in healthy men and women have suggested that high-sensitivity C-reactive protein (hs-CRP) level is a strong and independent risk predictor for future cardiovascular risk (5,6). Some experts advocate routine measurement of hs-CRP level as a part of cholesterol screening for overall evaluation of the cardiovascular risk (7,8). hs-CRP is increased by factors such as elevated blood pressure, elevated body mass index, cigarette smoking, metabolic syndrome/diabetes mellitus, low HDL/high triglycerides, estrogen/progesterone hormone use, and acute or chronic infections. However, hs-CRP is decreased by factors such as moderate alcohol consumption, excessive exercise, weight loss, and medications such as statin, fibrate, and niacin (9). Since these factors may be encountered frequently, accuracy of making conclusions based on the hs-CRP levels is controversial. In this study, frequency of the factors influencing hs-CRP levels and feasibility of routine hs-CRP evaluations in diabetic patients were evaluated.

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Materials and Methods

Ninety-one consecutive patients with type 2 diabetes mellitus admitted to the Diabetes Outpatient Clinic of Istanbul Göztepe Training and Research Hospital were enrolled in this study. Seventy (76.9%) of cases were receiving oral antidiabetics, and 9(9.8%), 8(8.7%) and 4(4.3%) cases were receiving oral antidiabetics plus insulin, insulin or only diet therapy, respectively. Local ethic committee and the patients were informed about this observational study protocol.

Factors influencing hs-CRP levels based on 2003 American Heart Association Guidelines were questioned (Smoking and alcohol drinking habits, physical activity and weight condition, concomitant medications such as hormone replacement therapy, use of statin, fibrate, angiotensin-converting enzyme inhibitor, aspirin and glitazone) (9). A detailed physical examination was performed and 12-lead electrocardiography recordings were obtained in all the patients.

Sitting blood pressure was measured from both arms with an appropriate mercury sphygmo-manometer after at least 10 minutes of rest, based on Korotkoff Phase I and Phase V sounds. Blood pressure measurement was repeated and recorded at least 3 minutes later from the arm with the higher value. An average of these two measurements was taken for systolic and diastolic blood pressure values. Anthropometric measurements (height, weight, waist circumference) were performed with standard devices by the same person when the patient was standing with regular cloths. The body mass index (BMI) was calculated using Quetlet's index (weight/height^2 - kg/m^2) (10). Those cases with a BMI $\geq$30 kg/m^2 were considered as obese, while those with a BMI between 25 and 29.9 kg/m^2 were considered as overweight. Waist circumference was measured at the midline between arcus costarum and crista iliaca anterior superior and at the narrowest torso circumference, during the patient was standing and slightly expiring.

Patients were evaluated in terms of metabolic syndrome according to the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) criteria (blood pressure $\geq$ 130/85 mm Hg (or current antihypertensive use); fasting plasma glucose $\geq$ 110 mg/dL (or current antidiabetic use); fasting triglycerides $\geq$ 150 mg/dL; HDL-cholesterol < 40 mg/dl (men) or < 50 mg/dl (women); and waist circumference > 102 cm (men) or > 88 cm (women)) (11).

Venous blood samples were taken for blood chemistry parameters after 12-hours of fasting, and the sera were immediately separated by centrifuging at 2500 rpm. Glucose, HDL-cholesterol, and triglyceride levels were measured through enzymatic assay, using an Olympus AU 5200 autoanalyser.

Statistical analyses of the results were performed as frequency percent and absolute numbers of factors.

Results

Fifty-six of 91 enrolled patients were female (mean age: 51.4±8.8 years), and 35/91 were male (mean age: 57.2±11.3 years). Table 1 demonstrates distribution of factors influencing hs-CRP levels in the patients.

Table 1. Distribution of factors effecting hs-CRP levels among patients

	Female (n=56)	Male (n=35)
Factors increasing hs-CRP		
BMI (mean±SD)	29.34±5.157	28.3±3.88
Hypertension (n, %)	44 (78.5)	29 (82.8)
Metabolic syndrome (n, %)	49 (87.5)	25 (71.4)
Low HDL (n, %)	39 (69.6)	14 (40)
High triglycerides (n,%)	28 (50)	18 (51.4)
Factors decreasing hs-CRP		
Alcohol (n, %)	1 (1.7)	4 (11.4)
Excessive exercise (n, %)	1 (1.7)	8 (22.8)
Weight loss (n, %)	10 (17.8)	4 (11.4)
Drugs (n, %)		
Statin	11 (19.6)	3 (8.5)
Fibrate	4 (7.1)	2 (5.7)
ACEI's	26 (46.4)	10 (28.5)
Aspirin	7 (12.5)	7 (20)
Glitazone	-	2 (5.7)

BMI, Body mass index; ACEI, angiotensin converting enzyme inhibitor

For female patients, frequencies of non-metabolic factors increasing hs-CRP levels such as smoking,

hormone replacement therapy, acute infections and chronic infections were 14.2%, 3.2%, 7.1% and 3.5%, respectively. For male patients, corresponding figures were 14.2%, 8.5% and 5.7% for smoking, acute infections and chronic infections, respectively.

Overall, 16.4% of patients had at least one factor increasing hs-CRP level (17,8 in females; 14,2 in males; Table 2).

Table 2. Frequency of non-metabolic factors increasing hs-CRP among patients

	Female (n=56)	Male (n=35)	All patients (n=91)
Smoking (n, %)	8 (14.2)	5 (14.2)	13 (14.2)
Using estrogen or progesteron (n, %)	3 (5.3)	-	3 (3.2)
Acute infection (n, %)	4 (7.1)	3 (8.5)	7 (7.6)
Chronic infection (n, %)	2 (3.5)	2 (5.7)	4 (4.3)
Patients with at least one factor (n, %)	10 (17.8)	5 (14.2)	15 (16.4)

Discussion

In this study, we have found at least one additional factor increasing hs-CRP level other than metabolic causes, in significant amounts of patients with type 2 diabetes mellitus. If the risk of cardiovascular disease is to be evaluated on the basis of serum hs-CRP level, there should be no other condition influencing this level. However, one sixth of our patients admitted for routine daily practice were not included in this category.

Growing evidence suggests that serum hs-CRP concentration is an important risk factor for cardiovascular diseases and does have prognostic significance in patients with coronary artery disease (12-14). Some experts recommend routine measurement of hs-CRP during cholesterol screening for the evaluation of overall cardiovascular risk (7). However, possible mechanisms of the relationship between hs-CRP and cardiovascular disease are not clear. In addition, certain factors about routine hs-CRP measurement, such as feasibility and cost-effectiveness of the test, should be considered (15,16).

Given the low specificity of this test, how hs-CRP levels will be evaluated? CRP is an acute phase reactant, which increases in many inflammatory disorders (17). When there is not any specific cause, high levels may only be regarded as weak predictors.

It was recommended that serum hs-CRP measurement should be added into a modified version of Framingham Risk Points for the evaluation of cardiovascular risk (18). However, in a joint report of Centers for Disease Control and Prevention (CDC) and American Heart Association (AHA) published at 2003, such a wide role for CRP measurement was not supported. In this publication, low, moderate, and high risk levels were defined as <1, 1 - 3, and >3 mg/l, respectively, and repetition of the measurements higher than 10 mg/l and investigation of the patient for infection and inflammation were recommended. In the same report, hs-CRP measurement was highlighted as not being recommended as a screening test in individuals with low cardiovascular risk, because of lacking adequate evidence (9).

Should management be modified based on CRP levels? There is not a specific therapy for the reduction of serum CRP levels, and no evidence suggests that reducing CRP will decrease the cardiovascular risk (19). Many of the concurrent medicines influence hs-CRP level (20-25). In our study, more than half of our patients were using at least one medicine reducing hs-CRP level, for various reasons. CDC-AHA report has concluded that secondary prevention measures would not require determining serum hs-CRP levels, and using serial hs-CRP measurements for evaluating therapeutic efficacy would be inaccurate (9).

In conclusion; factors influencing hs-CRP levels are frequently present in patients admitting to diabetes outpatient clinic, suggesting that using hs-CRP as a predictor for cardiovascular risk will be of limited value for outpatient clinics.

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