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Original Article

Clinical significance of hypertension, diabetes and inflammation, as predictor of cardiovascular disease

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ABSTRACT

Despite the availability of effective primary and secondary therapies, cardiovascular disease (CVD) remains the leading cause of morbidity and mortality. Use of traditional cardiovascular risk factors is imprecise and predicts less than one half of future cardiovascular events. Diabetes generally results in early death from CVD. Hypertension also increases the risk of CVD. Patients with hypertension and diabetes with accompanied dyslipidemia are soft targets of cardiovascular deaths. The growing appreciation of the role of inflammation in atherogenesis has focused attention on whether circulating levels of inflammatory biomarkers may help identify those at risk of future cardiovascular events. High-sensitivity C-reactive protein (hsCRP) has been investigated extensively as a marker of inflammatory response that is useful in predicting the risk of CVD. The role of hsCRP and the combined effect of diabetes and hypertension in the prediction of risk of CVD is less defined. The present study was therefore designed to evaluate the association of hsCRP, diabetes and hypertension in the prediction of risk of CVD. Hundred patients were recruited for the study, of which, fifty belongs to control and fifty were test group. For the entire study population hsCRP, sugar level, hypertension and lipid profiles were measured. Considerable variability was observed between control and test group. Among the patients with complications (diabetes and hypertension), there was a significant elevation of hsCRP and lipid profile than the control. It was found that the measurement of hsCRP in CVD patients with diabetes and hypertension may prove to be even a better marker of risk response.

1. Introduction

Early detection and treatment of hypertension, hypercholesterolemia, diabetes and smoking, have substantially reduced the incidence of cardiovascular deaths [1]. Despite the yearly decline in mortality, CVD remains the first cause of death [2]. Therefore it is essential to improve their prevention, in particularby putting into practice the progresses concerning diagnosis of high CVD and stroke risk that exposes to increase their probability (three or four more times than normal) in the next ten years. Some studies have shown that serum high-sensitivity C-reactive protein (hsCRP) measurements are predictive of cardiovascular ischemia and death in patient populations with angina or acute coronary syndrome (ACS) [3]. In some institutions, hsCRP levels are also monitored in hospitalized patients with angina symptoms. Elevated levels of hsCRP in healthy patients

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have been found to be predictive of a first cardiac event and are useful in identifying patients at increased risk for a cardiac event [4, 5]. Several recently published studies have described the utility of hsCRP evaluation in the secondary prevention of cardiovascular events [6, 7, 8]. The objective of the present study is to describe the role of hsCRP as a marker of risk for CVD to the primary care provider.

2. Materials and Methods

2.1. Patients

The total number of patients included in this study was 100. At the time of admission or entrance all patients responded to a standardized questionnaire covering many personal details (such as smoking habit, alcohol intake, physical activity, food habit, family history, and medical information) organised by trained interviewers. The study population consisted of 50 patients (test group) with a mean age of 58.28±9.3 years; the control group included 50 patients with mean age of 55.1±6.4 years.

2.2. Biochemical parameters and Assay

Samples for the analysis of lipid profile were obtained in the fasting state. The venous blood samples were drawn into pyrogen-free blood collection tubes without additive. The serum was collected after centrifugation at 3500 rpm for 3 minutes and then stored at in a refrigerator until analyzed. Samples were collected from the lab for further analysis. Total cholesterol (TC) and triglycerides (TG) were assayed by routine enzymatic methods using an auto analyser. High-density lipoprotein (HDL) cholesterol was measured using the same enzymatic method after precipitation of the plasma with phosphotungstic acid in the presence of magnesium ions. For cost reasons, LDL cholesterol values have long been estimated using the Friedewald formula: [TC] - [total HDL cholesterol] - 20% of the TG value = estimated LDL cholesterol. The VLDL cholesterol is estimated as one-fifth of the TG. The concentration of hsCRP was measured in serum by the latex-enhanced immunoturbidimetric method.

2.3. Statistical Analysis

Statistical analysis was performed with SPSS 12 statistical software package. Data were recorded on a pre-designed proforma and managed on spreadsheet. All the entries were checked for any error. Descriptive statistics for quantitative variables were computed by mean and standard deviation. Means in the two groups were compared by Student's t-test. In this study, $p<0.05$ has been considered as statistically significant.

3. Results

Table 1 shows the clinical characteristics of the study patients. The mean age in test ($p< 0.006$) was higher in patients than the control with statistically significant differences. The percentage of the study population over 65 years was (6%) and (22%) in control and test group respectively.

Table 1. Clinical characteristics of the study subjects (Non-modifiable and modifiable risk factors

	Control (n=50	Test group (n=50)
Non-modifiable risk factors		
Age	55.08 6.4	58.28 9.3
Age >65	3(6%)	11(22%)
Sex M/F	29/21	33/17
Cigarette smoking	4(8%)	8(16%)
Obesity	1(2%)	4(8%)
Physical inactivity	44(88%)	46(92%)
Modifiable risk factors		
Hypertension	16(32%)	16(32%)
Hypertension (M/F)	10/6	13/3
Hypertension age >50	14(28%)	12(24%)
Hypertension + High hsCRP	8(16%)	14(28%)
Diabetes	11(22%)	27(54%)
Diabetes (M/F)	7/4	19/8
Diabetes age >50	18(36%)	23(46%)
Diabetes + High hsCRP	6(12%)	19(38%)
Hypertension + Diabetes /Age >50	3(6%)	7(14%)
Hypertension + Diabetes	4(8%)	10(20%)
Atherogenic dyslipidemia	1(2%)	12(24%)
Metabolic syndrome	4(8%)	17(34%)
Hypercholesterolemia	10(20%)	22(44%)
Hypertriglyceridemia	16(32%)	27(54%)
Low-HDL cholesterolemia	20(40%)	39(78%)
High-LDL cholesterolemia	6(12%)	17(34%)

Cardiovascular risk factors including smoking, obesity, hypertension and diabetes had a higher prevalence in the test group than in control. Smoking was significantly higher in test group (16%) than control (8%). Obesity (BMI 30 kg/m) was significantly higher in test group (8%) than control (2%). Physical inactivity was also higher in test group than in control 92% and 88% respectively. 34% in test group and 8% in control group were affected by metabolic syndrome. Of the people examined 32% in control and 32% in test group had BP levels of 140 or 90 or higher. The prevalence of hypertension was higher in test group than control. The mean BP was significantly higher in test group ($p< 0.08$) than control. The occurrence of hypertension was significantly higher in people aged 50 years and over in control (28%) and test group

(24%). In control 10 males and 6 females and in test group 13 males and 3 females were suffered from hypertension. History of diabetes was significantly higher for test group (54%) (p< 0.001) than for control (22%). The occurrence of diabetes was significantly higher in people aged 50 years and over in control (36%) and test (46%). In control 7 males and 4 females and in test group 19 males and 8 females were suffered from diabetes. The occurrence of diabetes and hypertension were significantly higher in people aged 50 year and over in control (6%) and in test group (14%).

The patients had significant higher concentration of mean hsCRP levels in group test group (p< 0.001) when compare with the healthy control group. The prevalence of hsCRP in patients suffered from diabetes found to be in control (12%) and in test group (38%). The occurrence of hsCRP in hypertension found to be in control (16%) and in test group (28%). Risk of CVD increased significantly with increasing TC and LDL cholesterol. The percentage of hypercholesterolemia was higher in test group (44%) than control (20%). There was statistically significant difference between control and test group (p< 0.001). The prevalence of high LDL cholesterolemia was higher in test group (34%) when compared with control (12%). There was a significant difference between control and test group (p< 0.001). Hypertriglyceridemia was significantly higher in test group (54%) than control (32%). There was significant difference between control and test group (p< 0.04). There was significant difference found between VLDL cholesterol in control and test group (p< 0.05). Low-HDL cholesterolemia was higher in test group (78%) than control (40%). There was statistically significant difference between test group with control (p< 0.002) (Table 2).

Table 2. Baseline mean level of the biochemical parameters examined in serum samples of all the patients

	Control (n=50	Test group (n=50)
Non-lipid risk factor /risk markers		
Systolic BP	123.8 11.6	128.0 12.9
Diastolic BP	81.2 7.7	83.8 7.5
High-sensitivity C-reactive protein	0.9 0.4	1.8 1.4
Glucose	114 20.9	143.6 54.9
Lipid risk factor		
Total cholesterol	166.0 30.8	196.9 39.2
Triglycerides	137.7 71.3	173.8 88.0
High-density lipoprotein cholesterol	40.1 6.8	35.7 6.3
Low-density lipoprotein cholesterol	98.9 26.9	126.4 33.0
Very low-density lipoprotein cholesterol	27.8 14.7	34.8 17.7

4. Discussion

The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP [9, 10] defines categorical hypertension as a BP 140 mmHg systolic or 90 mmHg diastolic or current use of antihypertensive medication. Numerous observational studies have demonstrated unequivocally a powerful association of high BP with risk for CHD [11, 12, 13]. This association holds for men and women and younger and older persons. Even below categorical hypertension, subjects with high-normal BP (130–139 mmHg systolic and/or 85–89 mmHg diastolic) are at increased risk for CHD compared with those with optimal values [14, 15]. Clinical trials have established that BP reduction in people with hypertension reduces risk for a variety of BP-related endpoints including CHD [16]. This is true even for older people with isolated systolic hypertension [17].

Diabetes is defined as fasting blood glucose of 126 mg/dL or greater [18]. Risk for all forms of CVD, including CHD is increased substantially with type 1 and type 2 diabetes mellitus [19, 20]. Furthermore, the mortality rate in diabetic subjects who have experienced CHD is much higher than in non-diabetic subjects [21, 22]. The increase in risk attributed to hyperglycemia per se is independent of the overweight/obesity and dyslipidemia commonly observed in persons with diabetes. Tighter glycemic control reduces risk for microvascular complications of diabetes such as renal impairment and retinopathy. Thus far, however, improved glucose control in diabetic people has not been definitively shown to reduce macrovascular disease (CHD), although a trend toward benefit has been observed [23].

A seminal study by Liuzzo et al., [24] found that patients presenting with unstable angina and elevated plasma levels of hsCRP and SAA had a higher rate of adverse coronary outcomes than did patients without elevated levels of inflammatory markers, even in the absence of troponin elevation. Data from the Thrombolysis In Myocardial Infarction (TIMI) investigators indicate that the increased cardiac risk associated with high hsCRP levels may be evident as soon as 14 days after presentation with an ACS [25]. The Chimeric c7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment (CAPTURE) trial of the glycoprotein IIa/IIIb inhibitor abciximab found that, although not predictive in the initial 72-hour period, hsCRP predicted risk of mortality or MI at 6 months [26] and at 4 years [27]. Among patients in the FRagmin during InStability in Coronary artery disease (FRISC) trial of low-molecular weight heparin, the risk associated with elevated hsCRP levels at the time of the index event (unstable angina in 61% and MI in 39% of participants) continued to increase during a 3-year follow-up period [28]. To assess the clinical utility of testing for hsCRP among patients with ACS, it is necessary to evaluate the predictive value of hsCRP in relation to established biochemical markers of MI.

In the TIMI, CAPTURE, and FRISC studies, the predictive value of hsCRP was shown to be independent of, and additive to, troponin. Thus, hsCRP has prognostic value even in patients without evidence of myocyte necrosis. A multimarker approach using hsCRP, troponin I, and B-type natriuretic peptide has been shown to improve risk prediction in patients with ACS [29]. Among 450 patients in the TIMI trial who were categorized on the basis of the number of elevated biomarkers at presentation, there was a near doubling of the 30-day mortality risk for each additional

biomarker that was elevated. Similar relations also existed for the endpoints of MI and congestive heart failure, and for the composite of the 3 outcomes, at 30 days and at 10 months. In a validation cohort, the number of elevated biomarkers remained a significant predictor of the composite outcome; after adjustment for confounders, compared with those with no elevated biomarkers, patients with 1, 2, and 3 elevated biomarkers had 2.1, 3.1, and 3.7 times the risk, respectively, of experiencing the composite endpoint by 6 months.

Nine risk factors were found to account for over 90% of the risk of first MI in a study of over 12,000 cases of MI: [30] dyslipidemia, smoking, hypertension, diabetes, abdominal obesity, depression and other psychosocial factors, low levels of physical activity, low levels of fruit and vegetable consumption, and low levels of alcohol consumption. It is thus reasonable to conclude that hsCRP predicts coronary events merely because it is associated with the major risk factors for atherosclerosis. This conclusion is supported by the recent report that increased hsCRP was largely attributable to conventional CHD risk factors in an Australian population study [31]. Michowitz et al., [32] studied the predictive role of hsCRP in patients with diastolic heart failure. They concluded that hsCRP concentrations are elevated in patients with diastolic heart failure and correlate with disease severity.

5. Conclusion

This study point out that both hypertension and diabetes were proven as independently associated with an increased risk of the incidence of CVD. Detection of hsCRP should be given consideration while assessing cardiovascular risk in order to better evaluate the risk of atherosclerotic vascular disease especially in patients with a hyperlipidemia, hypertension and diabetes an early CVD.

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