ISSN: 0975-3583,0976-2833 VOL13, ISSUE 07, 2022

A STUDY ON CLINICAL IMPORTANCE OF HYPERTENSION, DIABETES, AND INFLAMMATION AS INDICATORS OF CARDIOVASCULAR DISEASE.

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Received Date: 26/03/2022 Acceptance Date: 07/07/2022 Publish Date: 14/10/2022

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ABSTRACT

Background: Cardiovascular disease (CVD) continues to be the foremost cause of morbidity and mortality, despite the existence of effective primary and secondary treatment options. Traditional cardiovascular risk factors are often inadequate, predicting less than half of future cardiovascular incidents. Diabetes typically leads to premature mortality due to CVD, while hypertension further exacerbates this risk. Individuals suffering from both hypertension and diabetes, particularly when accompanied by dyslipidemia, are particularly vulnerable to cardiovascular-related fatalities. Recent research has increasingly highlighted the significance of inflammation in the development of atherosclerosis, prompting investigations into whether circulating inflammatory biomarkers can aid in identifying individuals at heightened risk for future cardiovascular events. High-sensitivity C-reactive protein (hsCRP) has been extensively studied as an inflammatory marker that may be instrumental in assessing CVD risk. However, the specific role of hsCRP, particularly in conjunction with diabetes and hypertension, in predicting CVD risk remains less clearly defined. Consequently, this study aimed to explore the relationship between hsCRP levels, diabetes, and hypertension in predicting CVD risk. A total of one hundred patients were enrolled, with fifty in the control group and fifty in the test group. Measurements of hsCRP, blood sugar levels, hypertension, and lipid profiles were conducted for the entire study cohort. Notable differences were observed between the control and test groups. Among patients with complications such as diabetes and hypertension, there was a significant increase in hsCRP levels and lipid profiles compared to the control group. The findings suggest that measuring hsCRP in CVD patients with diabetes and hypertension may serve as a more effective marker for assessing risk.

INTRODUCTION

The early identification and management of hypertension, hypercholesterolemia, diabetes, and smoking have significantly decreased the rate of cardiovascular-related fatalities. Nevertheless, despite the annual reduction in mortality rates, cardiovascular disease (CVD) continues to be the leading cause of death. Consequently, it is crucial to enhance preventive measures, particularly by implementing advancements in the diagnosis of elevated CVD and stroke risk, which can increase the likelihood of these events occurring three to four times more than the

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 07, 2022

average over the next decade. Research has indicated that serum high-sensitivity C-reactive protein (hsCRP) levels can predict cardiovascular ischemia and mortality in patients with angina or acute coronary syndrome (ACS). In certain healthcare facilities, hsCRP levels are routinely monitored in hospitalized patients presenting with angina symptoms. Elevated hsCRP levels in otherwise healthy individuals have been associated with an increased risk of experiencing a first cardiac event, thereby aiding in the identification of patients at heightened risk. Numerous recent studies have highlighted the importance of hsCRP assessment in the secondary prevention of cardiovascular incidents. The aim of this study is to elucidate the significance of hsCRP as a risk marker for CVD for primary care providers.

MATERIALS AND METHODS

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.

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.

Statistical Analysis

Statistical analysis was performed with r tool 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.

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.

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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	58.28
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 such as smoking, obesity, hypertension, and diabetes were found to be more prevalent in the test group compared to the control group. The incidence of smoking was notably higher in the test group at 16%, in contrast to 8% in the control group. Similarly, obesity, defined as a BMI of 30 kg/m² or greater, was significantly more common in the test group (8%) than in the control group (2%). Additionally, physical inactivity was reported at higher rates in the test group (92%) compared to the control group (88%). Metabolic syndrome affected 34% of individuals in the test group, while only 8% of those in the control group were impacted. Among the participants, 32% in both the control and test groups exhibited blood pressure levels of 140/90 mmHg or higher, indicating a greater prevalence of hypertension in the test group. The mean blood pressure was significantly elevated in the test group ($p < 0.08$) compared to the control group. Furthermore, the incidence of hypertension was notably higher among individuals aged 50 years and older, with rates of 28% in the control group and 24% in the test group. In terms of gender distribution, the control group included 10 males and 6 females with hypertension, while the test group had 13 males and 3 females affected. The history of diabetes was significantly more prevalent in the test group (54%, $p < 0.001$)

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compared to the control group (22%). Among those aged 50 years and older, the occurrence of diabetes was higher in the control group (36%) than in the test group (46%). The control group reported 7 males and 4 females with diabetes, while the test group had 19 males and 8 females affected. The rates of both diabetes and hypertension were significantly elevated in individuals aged 50 years and older, with occurrences of 6% in the control group and 14% in the test group. The patients exhibited a markedly higher mean concentration of hsCRP levels in the test group ($p< 0.001$) compared to the healthy control group. The prevalence of hsCRP among patients with diabetes was recorded at 12% in the control group and 38% in the test group. For those with hypertension, the prevalence was 16% in the control group and 28% in the test group. The risk of cardiovascular disease (CVD) showed a significant increase with elevated total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol levels. The incidence of hypercholesterolemia was notably greater in the test group at 44%, in contrast to 20% in the control group, with a statistically significant difference observed ($p< 0.001$). Furthermore, the prevalence of high LDL cholesterolemia was higher in the test group at 34% compared to 12% in the control group, also demonstrating a significant difference ($p< 0.001$). Hypertriglyceridemia was significantly more prevalent in the test group at 54% than in the control group at 32%, with a significant difference noted ($p< 0.04$). Additionally, a significant difference was identified in VLDL cholesterol levels between the control and test groups ($p< 0.05$). Low-HDL cholesterolemia was more prevalent in the test group at 78% compared to 40% in the control group, with a statistically significant difference ($p< 0.002$) (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	128.0
Diastolic BP	81.2	83.8
High-sensitivity C-reactive protein	0.9	1.8
Glucose	114.2	143.6
Lipid risk factor		
Total cholesterol	166.0	196.9
Triglycerides	137.7	173.8
High-density lipoprotein cholesterol	40.1	35.7
Low-density lipoprotein cholesterol	98.9	126.4
Very low-density lipoprotein cholesterol	27.8	34.8

DISCUSSION

The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure defines categorical hypertension as a systolic blood pressure of 140 mmHg or higher, a diastolic blood pressure of 90 mmHg or higher, or the current use of antihypertensive medications. Numerous observational studies have clearly established a strong correlation between high blood pressure and the risk of coronary heart disease. This

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 07, 2022

relationship is consistent across both genders and among individuals of varying ages. Furthermore, individuals with high-normal blood pressure, defined as a systolic pressure between 130 and 139 mmHg and/or a diastolic pressure between 85 and 89 mmHg, also face an elevated risk for coronary heart disease when compared to those with optimal blood pressure levels. Clinical trials have confirmed that lowering blood pressure in hypertensive individuals decreases the risk of various blood pressure-related outcomes, including coronary heart disease. This finding is applicable even to older adults with isolated systolic hypertension.

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 pivotal investigation conducted by Liuzzo *et al*. [24] revealed that patients experiencing unstable angina with elevated plasma concentrations of hsCRP and SAA exhibited a greater incidence of adverse coronary events compared to those without heightened inflammatory markers, even in the absence of troponin elevation. Findings from the Thrombolysis In Myocardial Infarction (TIMI) study group suggest that the augmented cardiac risk linked to elevated hsCRP levels may manifest as early as 14 days following the presentation of an acute coronary syndrome (ACS) [25]. The Chimeric c7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment (CAPTURE) trial, which evaluated the glycoprotein IIa/IIIb inhibitor abciximab, indicated that while hsCRP was not a predictor in the initial 72 hours, it did forecast the risk of mortality or myocardial infarction at both 6 months [26] and 4 years [27]. In the FRagmin during InStability in Coronary artery disease (FRISC) trial involving low-molecular weight heparin, the risk associated with elevated hsCRP levels at the time of the initial event (unstable angina in 61% and myocardial infarction in 39% of participants) continued to escalate over a 3-year follow-up period [28]. To determine the clinical relevance of hsCRP testing in patients with ACS, it is essential to assess its predictive value in comparison to established biochemical markers of myocardial infarction.

In the TIMI, CAPTURE, and FRISC studies, the independent and additive predictive value of high-sensitivity C-reactive protein (hsCRP) in relation to troponin was established. Consequently, hsCRP demonstrates prognostic significance even in patients lacking evidence of myocyte necrosis. A multimarker strategy incorporating hsCRP, troponin I, and B-type natriuretic peptide has been shown to enhance risk assessment in individuals with acute coronary syndrome (ACS). Within the TIMI trial, among 450 patients classified by the number of elevated biomarkers at initial presentation, the risk of 30-day mortality nearly doubled with each additional elevated biomarker. Similar associations were observed for myocardial infarction (MI), congestive heart failure, and the composite of these three outcomes, both at 30 days and at 10 months. In a validation cohort, the count of elevated biomarkers continued to serve as a significant predictor of the composite outcome; after adjusting for confounding variables, patients with one, two, and three elevated biomarkers faced risks of 2.1, 3.1, and 3.7 times greater, respectively, of reaching the composite endpoint within six months compared to those with no elevated biomarkers. A study involving over 12,000 cases of myocardial infarction identified nine risk factors that accounted for more than 90% of the risk for a first

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 07, 2022

MI: dyslipidemia, smoking, hypertension, diabetes, abdominal obesity, depression and other psychosocial factors, low physical activity levels, insufficient fruit and vegetable intake, and low alcohol consumption. Therefore, it is reasonable to infer that hsCRP's predictive capability for coronary events is primarily due to its association with the principal risk factors for atherosclerosis. This inference is further supported by a recent Australian population study indicating that increased hsCRP levels were largely linked to conventional coronary heart disease (CHD) risk factors. Additionally, Michowitz *et al.* investigated the predictive significance of hsCRP in patients with diastolic heart failure, concluding that hsCRP concentrations are elevated in this patient group and correlate with the severity of the disease.

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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