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Role of High Sensitivity C Reactive Protein and Interleukin -6 in Cardiovascular Disease

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Abstract

The study comprised of 100 patients with known history of CVD compared with 100 control healthy subjects. We investigated the levels of fasting lipid profile and inflammatory markers as hs C-reactive protein and interleukin-6 in patients with cardiovascular disease andcompared with control subjects. The fasting lipid profile were found significantly raised (p<0.0001) except HDL-C in CVD patients than control subjects. The levels of serum hs CRP and IL-6 were also found significantly higher (p<0.0001) in cardiovascular disease compared to control subjects.In conclusion, measurement of C-reactive protein and interleukin-6 may be useful in predicting a patient's risk of future cardiovascular events.

Keywords: Cardiovascular disease, Lipid profile, Hs-CRP, IL-6.

Introduction

Inflammation leads to the localized recruitment of neutrophils and monocytes, and the presence of activated macrophages in the cap of the atherosclerotic plaque[1] has led to suggestions that they contribute to plaque rupture through effects on matrix metallo-proteinases. The hepatic synthesis of CRP is largely under the regulation of the pro-inflammatory cytokine IL-6. This cytokine is unusual, in that its major effects take place at sites distinct from its origin and are consequent upon its circulating concentrations. IL-6 is a circulating cytokine known to be secreted from a number of different cells including activated macrophages and lymphocytes. The biological activities of IL-6 are initiated by binding to a high-affinity receptor complex, consisting of two membrane glycoproteins[2]. Previous studies have estimated the severity of inflammation by use of circulating C-reactive protein levels. However, C-reactive protein is a product of the acute phase reaction[3] and because the concentration of C-reactive protein may be subject to post transcriptional regulation[4]. C-reactive protein may not measure all of the relevant effectors of inflammation. Interleukin-6 is the major initiator of the acute phase response by hepatocytes and induces the synthesis of C- reactive protein, as well as other acute phase reactants[3]. C-reactive protein, a sensitive marker of inflammation, has been proposed as an independent risk factor for cardiovascular disease. In the present study we compared the levels of hs C-reactive protein and interleukin-6 in cardiovascular disease with control healthy subjects.

Material and Methods

The total no (n=100) of patients with known history of cardiovascular disease, who attended OPD of MY Hospital, included into the study. Persons who do not have any abnormal medical history, included as control subject (n=100). After obtaining informed consent, a questionnaire that contained demographic characteristics including age, sex, cardiovascular risk factors and drug history was completed. Patient's weight, height, BP were measured and recorded. The majority of patients (82%) hypertensive and (56%) diabetic; they were taking antihypertensive, cholesterol lowering and glycemic control medication at the time of the study. Patients who had hormonal disorders, HIV-positive status, liver disorder, renal or thyroid disorder, presence of any acute inflammatory conditions that includes infections, trauma or fever were excluded from the study. After 12 hours fasting blood samples collected in the clinical biochemistry laboratory were used for in vitro biochemical analysis. Hs C-reactive protein and interleukin-6 were measured using a commercially available ELISA Kit (Ray Biotech, Inc.). The lipid profiles were measured with enzymatic and using colorimetric methods.

Statistical Analysis

Data analysis was performed using the XLSTAT 2014 program with a value of p<0.001 considered significant. One-way analysis of variance (ANOVA) for repeated measures within a group was measured. Comparison of two groups was done by the Student's paired t-test. Results are expressed as MEAN SD.

Results and Discussion

Table-1 summarizes the values for all parameters in cardiovascular disease and control subjects. The noted patient's age group was significantly higher (p<0.0001) than control group. The measured BMI, WC and blood pressure category were also significantly higher (p<0.0001) to control group.

Lipid profile comprised of total cholesterol, triglycerides, low density lipoprotein and very low density lipoprotein were found raised in figure-1 while high density lipoprotein was low, all were significantly($p<0.0001$) so. Other measured marker in figure-2 ashs CRP and IL-6levelswere found significantly ($p<0.0001$) increased from the base line in cardiovascular patients.

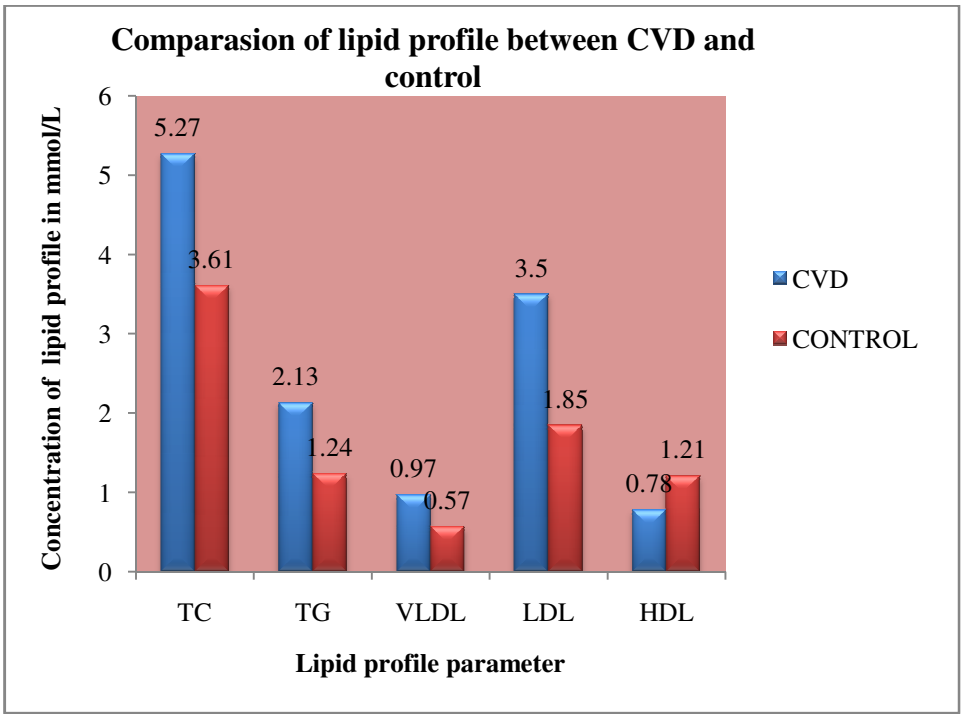

Figure-1
Comparisons of lipid profile between cardiovascular Patientsandcontrol Subject

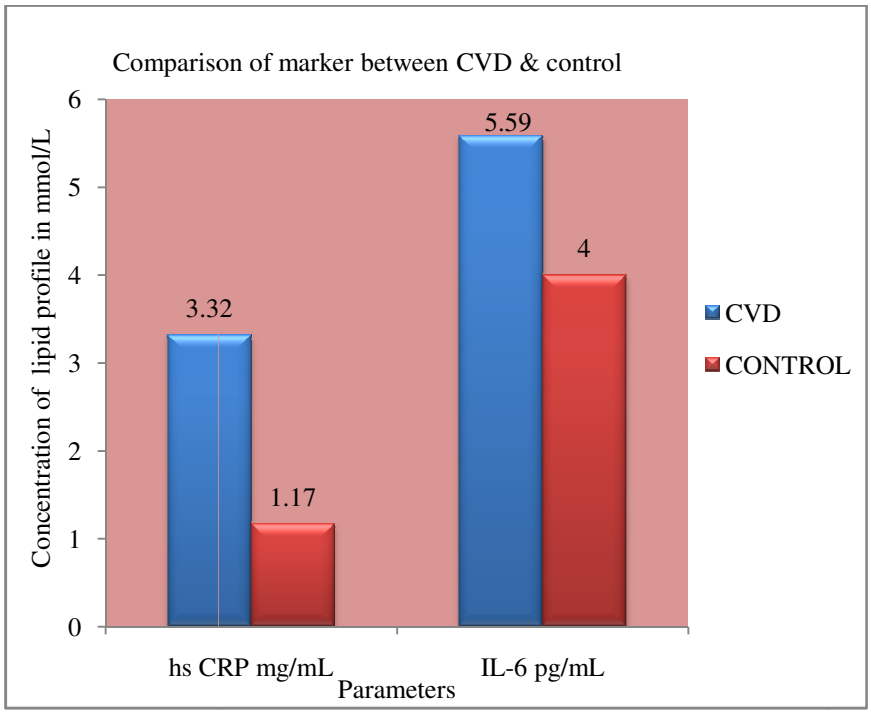

Figure-2
Comparisons of hs-CRP and IL-6 between cardiovascular patients and control subjects

Table-1
Anthropometric Measurement and Biochemical Variables of the Study Group

	CVD (n=100)	CONTROL (n=100)
AGE (YRS)	54.62±9.28	45.87±11.28
BMI (Kg/M^2)	26.72±2.43	22.02±2.77
WC (cm)	93.01±6.31	82.65±6.62
BPS (mm/Hg)	136.72±20.70	118.11±2.83
BPD (mm/Hg)	86.11±7.89	78.97 ±2.53
TC (mmol/L)	5.27±0.88	3.61±0.44
TG (mmol/L)	2.13±0.43	1.24±0.17
HDL (mmol/L)	0.78±0.11	1.21±0.18
LDL (mmol/L)	3.50±0.89	1.85± 0.45
VLDL (mmol/L)	0.97±0.20	0.57±0.07
hs-CRP (mg/mL)	3.32±0.57	1.17±0.25
IL-6 (pg/mL)	5.59±0.65	4.00±0.65

(TG mg/dl*0.0113TC, LDL, VLDL, HDL mg/dl*0.0259= mmol/L), All were significant P<0.0001 Values are expressed as mean SD

In the present study significantly (p<0.0001) deranged lipid profile (total cholesterol, low density cholesterol, very low density cholesterol and triglyceride) except high density cholesterol were found significant (p<0.0001) differences between cardiovascular patients than control group. It is a very known and agreed with several studies. It is widely accepted that cardiovascular disease is associated with hypertension and elevated blood levels of low-density lipoprotein (LDL), total cholesterol, and triglycerides. In contrast, a low level of high-density lipoprotein (HDL) is a risk factor for mortality from cardiovascular disease. Hyperlipoproteinemia is the lipid disturbance of major relevance clinically because of its association with an increased risk of atherosclerotic cardiovascular disease. Multiple epidemiologic studies have demonstrated that increased levels of plasma total cholesterol and low-density lipoproteins are strongly and directly related to a greater incidence of coronary heart disease. Elevated plasma triglycerides and very-low-density lipoproteins are directly associated with the risk of atherosclerotic heart disease, although not as independent risk factors. In contrast, high levels of high-density lipoprotein cholesterol have been found to be a protective factor for the development of that disease, so that decreased levels constitute a risk factor.

Inflammatory processes are major contributors to cardiovascular disease[5]. Interleukin-6 (IL-6) is known to be an inflammatory marker[6]. An increased serum level of IL-6 is associated with an increased risk of cardiovascular disease[7,8]. In our study, subjects with CVD had significantly high levels of hs C-reactive protein and interleukin-6 than control subjects. Volpato et al. reported the increased levels of inflammatory markers, including CRP and IL-6, have been demonstrated in patients with myocardial infarction and unstable and chronic stable angina[9,10], levels of IL-6 not only are associated with the severity of the conditions but also are very strong predictors of subsequent outcomes. Increased serum IL-6 levels are associated with CHD, stroke and cardiovascular mortality[11]. It has been reported that, during long-term follow-up, increased IL-6 levels are strongly associated with future cardiac events and mortality in a population with stable CHD[12]. Maeda et al.[13] reported that a high IL-6 level after optimized treatment for heart failure was an independent risk factor for morbidity and mortality in patients with congestive heart failure. Several authors reported the IL-6 has both pro-inflammatory and anti-inflammatory properties. It is produced not only by immune cells and immune accessory cells including monocytes and macrophages, but also by cardiovascular components, such as endothelial cells, vascular smooth-muscle cells, and ischemic myocytes[14,15], C - reactive protein (CRP) evokes the production of IL-6. A recent report from the Rural Health Study had shown that elevated concentrations of IL-6 predict total and cardiovascular mortality over a 5 year follow-up, the association being independent of prevalent vascular disease, smoking and traditional risk factors, and stronger than, but additive to, that for CRP[3].

The precise mechanisms underlying the interactions between high IL-6 levels and the incidence of cardiovascular events remain unclear. However, there are several mechanisms that could explain the relationship between these phenomena. Firstly, IL-6 is produced mainly by leukocytes, but partly also by cardiomyocytes and vascular endothelial cells[15, 16]. It has been reported that ischemic and hypoxic conditions stimulate IL-6 production[17]. Those reports suggest that elevated IL-6 levels at baseline might be induced by silent cerebral or myocardial ischemia. Secondly, IL-6 is a pleiotropic cytokine with a broad range of humoral and cellular immune effects related to inflammation[6]. Elevated IL-6 levels can contribute to the development and instability of atherosclerotic plaques by activation of leukocytes and endothelial cells or by the induction of various cytokines. Therefore, serum IL-6 levels might reflect the progression of vascular lesions. Thirdly, impaired autonomic neural activity has been recognized as a crucial risk factor for cardiac dysfunction, and is strongly associated with an increased risk for harmful events and overall mortality in DM patients[18,19].

Both laboratory and pathology data suggested that inflammation is important in atherosclerosis. Another study had demonstrated an association between elevated C-reactive protein levels and myocardial infarction in patients with stable or unstable angina[20], as well as in healthy men. The pathophysiology underlying the relation between C-reactive protein levels and cardiovascular disease is not understood. It has been suggested that C-reactive protein, a marker for systemic inflammation, may reflect chronic infection with organisms such as Chlamydia pneumoniae, Helicobacterpylori, orcytomegalovirus[21]. Atheromatous plaques infiltrated by inflammatory cells may be less stable than quiescent plaques because of collagen disruption from the effects of secreted metallo-proteinases. An alternative hypothesis would be that C- reactive protein is a marker for other proteins that are elevated during inflammation and that

increase coagulability. C-reactive protein enhances the expression of tissue factor by monocytes and is thus pro-coagulant. C-reactive protein also induces complement activation[22], leading to an increased inflammatory response that could increase the likelihood of lethal arrhythmias or the volume of ischemic tissue. C-reactive protein production by the liver is also stimulated by interleukin-6 and promotes leukocyte adhesion that results in enhanced recruitment of monocytes to atherosclerotic plaques, thus supporting thrombus formation[23].

Conclusion

In conclusion, measurement of C-reactive protein levels may be useful in predicting a patient's risk of future cardiovascular events. IL-6 level may improve risk stratification among patients suspected of having CAD. Patients with documented CVD and high hs-CRP and IL-6 levels should be followed, and there risk factors should be managed aggressively. These measures may be useful for identification of high-risk subgroups for anti-inflammatory interventions. Further research is needed to confirm the causality of association between serum IL-6 levels and CVD patients.

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