Comparison Between Serum hsCRP and LDL Cholesterol for Search of a Better Predictor for Ischemic Heart Disease

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Abstract Acute myocardial Infarction is one of the major causes of morbidity & mortality in world and atherosclerosis is the major cause of ischemic heart disease. In order to determine the better clinical marker of atherosclerosis, we estimated serum low-density lipoprotein (LDL-C) and high sensitivity C-reactive protein (hsCRP). Hundred patients of myocardial infarction and 100 controls irrespective of age and sex were studied for these parameters over a period of 2 years. The statistical analysis showed that the serum hsCRP was significantly raised in myocardial infarction cases than controls ($P < 0.01$) but LDL-C was not ($P > 0.05$). We conclude that the serum hsCRP has better predictive value for risk of atherosclerosis.

Keywords Myocardial infarction · Atherosclerosis · hsCRP · LDL cholesterol

Introduction

Cardiovascular diseases are the major cause of death globally. About 29.2% of total global deaths result from various forms of cardiovascular disease of which about 50% are due to ischemic heart disease (IHD) [1]. The cause of IHD is the atherosclerosis. Atherosclerosis is a chronic inflammatory response of the arterial wall initiated by injury to the endothelium. Moreover, lesion progression is sustained by interaction between modified lipoproteins (e.g. oxidized LDL), lipid laden macrophage (foam cells), T-lymphocytes and the normal cellular constituents of the

arterial wall. Atherosclerosis is also characterized by thickening of the arterial wall, which protrudes into and obstructs the vascular lumen [2]. Growing evidences suggest that local and general inflammation has got an important role in formation, progression and rupture of atherosclerotic lesion [3, 4]. This paradigm has fuelled exponential interest in evaluating inflammatory markers of which high sensitivity C-reactive protein (hsCRP) has emerged as one of the most important. Low-density lipoprotein (LDL), which is called bad cholesterol, rich in cholesterol ester, participates in the atherosclerotic process. Dyslipidemia with particular reference to LDL cholesterol has also been considered as risk factor for development of atherosclerosis [5]. The present study aims to assess whether serum LDL-C or hsCRP is the better and useful marker of atherosclerosis.

Materials and Methods

The present study was conducted in the department of Biochemistry of Katihar Medical College, Katihar, Bihar. Hundred patients irrespective of age and sex and diagnosed as myocardial infarction (clinically and by ECG findings) were selected as case. All the cases were positive to cardiac specific troponin I test. The selected patients were from Katihar district and adjoining areas. Patients having any concomitant infection and recent history of trauma were not included in the study. The controls were selected from the healthy persons from same region. Both the cases and controls were selected by a simple random method. After noting the name, age and sex, venous samples were drawn after 12 h of overnight fasting. Serum was separated and assays were performed within 24 h. Serum hsCRP was measured by Sandwich enzyme linked immunosorbent

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assay (ELISA) [6]. Serum total cholesterol, triglyceride (TG) and high density lipoprotein (HDL) were assayed by Cholesterol Oxidase–peroxidase (CHOD–PAP), glycerol-3-phosphate oxidase (GPO), polyanion precipitation methods respectively using semi-auto analyser. Serum very low-density lipoprotein (VLDL) was calculated by dividing the value of TG by 5 and serum LDL was obtained by Friedewald equation [8]. The value of hsCRP > 3 mg/l [7] and for LDL cholesterol ≥ 160 mg/dl [5] were considered as high risk for cardiovascular diseases. Using commercially available cardiac specific Trop I kit supplied by Zydus Company did troponin I test. It implies the principle of immuno chromatography and the sensitivity of test is serum cardiac specific troponin I value at 0.5 ng/ml. The data for biochemical analysis was subjected to standard statistical analysis such as Student's *t* test using the Statistical Package for Social Science (SPSS) 11.5 software.

Results

The personal profiles and clinical parameters of all the subjects under study are shown in Table 1. Low-density lipoprotein-C concentration in control group ranged from 68 to 129 mg/dl with the mean value 91.6 mg/dl whereas in IHD cases it was from 62 to 126 mg/dl with mean at 94.30 mg/l. High sensitivity C-reactive protein concentration in control group ranged from 0.3 to 0.9 mg/l with the mean value 0.5910 mg/l whereas in IHD cases it was from 2 to 5.8 mg/l with mean at 3.6590 mg/l. Thus the concentration of hsCRP in serum in cases of IHD is significantly higher (3.6590 ± 0.73664) than controls (0.5910 ± 0.18808) ($P < 0.0001$) but differences in concentration of serum LDL-cholesterol between IHD cases and controls are not significant ($P > 0.05$) (Table 2). Table 3 shows the distribution of patients in different risk groups as predicted by hs-CRP concentration. 82% of cases are having hsCRP concentration of more than 3 mg/l.

Table 1 Personal profile and clinical details of healthy persons and patients suffering from myocardial infarction

	Healthy persons	Patients suffering from myocardial infarction
Number of cases	100	100
Age	45.2 ± 8.6	44.9 ± 7.0
Sex		
Males	46	44
Females	54	56
Qualitative serum cardiac specific troponin I test	Negative	Positive

Table 2 Concentration of serum LDL-cholesterol and hsCRP in cases suffering from myocardial infarction and controls

Category	Concentration of serum LDL (mg/dl)	Concentration of serum hsCRP (mg/l)
IHD cases	94.30 ± 15.92057	3.6590 ± 0.73664
Control	91.60 ± 14.45159	0.5910 ± 0.18808
IHD cases vs. controls	$P > 0.05$	$P < 0.0001$

Values are mean $\pm$ SD; $P > 0.05$ not significant; $P < 0.0001$ highly significant

Table 3 Distribution of cases suffering from myocardial infarction according to their serum concentration of hsCRP in serum

Concentration of serum hsCRP (mg/l)	Total number of cases ($n = 100$)	
	Number of cases in each group	% of cases in each group
<1	0	0
1–3	18	18
>3	82	82

Discussion

Low-density lipoprotein is the most abundant lipoprotein in human, composed of core of neutral lipids, mainly cholesteryl ester, surrounded by a layer of phospholipids and held together by protein apo-lipoprotein B [9]. Low-density lipoprotein-C has been regarded as a causal and independent risk factor of atherosclerosis [10, 11]. But many studies have shown that factors other than total cholesterol and LDL-C must be considered when evaluating coronary artery disease (CAD) risks [12]. Recent studies have shown that the size of LDL particle is more important as compared to LDL-C concentration in atherogenesis [13, 14]. In routine clinical practice estimation of LDL particle size is not applicable due to complicated methodology [15]. All these factors lead to search for other cardio-vascular risk factors.

Inflammation plays a key role in the pathophysiology of atherosclerosis [16, 17]. The inflammatory cell types typically found in the atheroma include monocyte-derived macrophages and lymphocytes [18]. Macrophages present in the atherogenous plaque lead to the release of mediators like cytokines and chemokines which in turn increase the plasma concentration of CRP which amplify inflammatory and procoagulant responses [19]. Several other inflammatory markers for prediction of coronary accidents in healthy men and women and in patients with stable angina, acute coronary diseases and in follow up of cardiovascular accident have been studied. These markers include

interleukin (IL-6) [20, 21], serum amyloid A (SAA) [22], Tumour necrosis factor- α (TNF- α) [23], CD40 ligand [24]. Among these markers CRP has emerged as most powerful inflammatory marker of future cardiovascular risk [25–27]. C-reactive protein levels for normal adults are usually taken as <10 mg/l. C-reactive protein level may raise up to 1,000 folds in major infection and trauma. The level for predicting atherosclerotic event has been recommended as low risk at <1 mg/l, average at 1–3 mg/l and high risk at >3 mg/l [7]. To measure the CRP at such lower concentration high sensitivity assays have been developed, known as hsCRP. The hsCRP test has good precision, is done at a low cost, has good standardization and has least pre-analytical variances such as age, sex, diet and diurnal variance. In present study it is observed that the rise of hsCRP was highly significant as compared to control group ($P < 0.0001$). Several studies including Framingham Study have suggested that hsCRP has sufficient risk prediction value for atherosclerosis [28–30]. In present study it has also been shown that a very high percentage of myocardial infarction cases have serum hsCRP level more than 3 mg/l (82%), hence falling in high risk group whereas only 18% percent were having lower concentration (Table 3). It is interesting to note that in this study 100% of patients were having serum LDL-C concentration less than 160 mg/dl, which is the accepted high risk for CAD. This observation falls in accordance with findings of Willerson, who after extensive data analysis inferred that high CRP/Low LDL-C persons are at higher absolute risk than low CRP/high LDL-C persons [31]. However, it has been pointed out that CRP concentration has continuous association with the risk of coronary heart disease, ischemic stroke, vascular mortality and death from several cancers and lung diseases that are each of broadly similar size. The relevance of CRP to such a large range of disorders in some studies is unclear and it discriminates poorly between persons with coronary disease and those without [32, 33]. Therefore it has been suggested that patients with persistently unexplained, marked elevation of hs-CRP (>10 mg/l) after repeated testing should be evaluated for noncardiovascular etiologies (Class IIa, Level of Evidence B) [7].

Coronary artery disease patients who have not received any treatment show a significant rise in hs-CRP whereas after treatment a fall in its level has been observed [34]. Emerging evidences further suggest that hsCRP can be used to target pharmacological and lifestyle intervention design to prevent first as well as recurrent cardiovascular events. JUPITER trial was conducted to determine if patients with elevated CRP level without hyperlipidemia might benefit from statin therapy. The trial found that patients taking rosuvastatin with elevated CRP level experience a decrease in the incidence of major cardiovascular events [35, 36]. These trials also confirmed the

strong relationship between CRP with cardiovascular diseases. We can therefore conclude from our study that estimation of hsCRP can be considered as a better predictor for cardiovascular disease than the serum LDL-cholesterol. However, to designate serum hsCRP level as an independent risk factor more prospective studies are required.

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