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Original Research Article

High Sensitivity C-Reactive Protein and Low Density Lipoprotein Cholesterol in Risk Prediction of Ischemic Heart Disease

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ABSTRACT

Aims: To study the high sensitivity C-reactive protein and low density lipoprotein cholesterol in risk prediction of ischemic heart disease.

Methods: In the present study, 200 patients of IHD and 40 apparently healthy subjects were included and fasting blood parameters like lipid profile and hs-CRP were performed. Data were evaluated by applying student t test and sensitivity/specificity was also calculated.

Results: Levels of hs-CRP ($p<0.01$) and LDL-C ($p<0.05$) were significantly elevated in IHD patients than the control group but 55 patients of IHD had normal LDL-C, while their hs-CRP levels were significantly high. Furthermore, specificity and sensitivity of hs-CRP were also higher (100% & 85%) as compare to LDL-C (66% & 44%) in patients group.

Conclusion: The study demonstrated that the half of the IHD patients with normal LDL-C levels had significantly elevated levels of hs-CRP. Furthermore, in regard to sensitivity and specificity hs-CRP is far better predictor of IHD than LDL-C. Therefore, hs-CRP should be included in the standard protocol as a better and single predictor of IHD than conventional lipid profile which will improve the physician's ability for the early and better prediction of future occurrence of ischemic heart disease in patients.

Key words: Atherosclerosis, Cardiovascular Disease, hsCRP, Inflammation, Myocardial Infarction.

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INTRODUCTION

The role of inflammation in the pathogenesis of atherosclerosis has been firmly established in the past two decades. Various studies, both observational (nested case control and prospective cohort) and randomized controlled trials (RCTs) have shown an association of pro-inflammatory biomarkers with incident hypertension, metabolic syndrome, coronary artery disease (CAD), acute coronary syndrome (ACS), peripheral artery disease, stroke and recurrent coronary and cerebrovascular events.[1-4] Approx. 25 large observational studies published since the 1990s have established high sensitivity C-reactive protein (hsCRP), a biomarker of inflammation, as an independent predictor for CAD. A meta-analysis of these observational studies demonstrate that people in the top quartile for hsCRP levels had an odds ratio (OR) of 1.5 compared with those in the lowest quartile for major cardiovascular events, after adjusting for established risk factors.[5] Apart from observational studies, several RCTs evaluating statins such as Pravastatin or Atorvastatin Evaluation and Infection Therapy– Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI-22)[6], Cholesterol and Recurrent Events (CARE)[7], The Pravastatin Inflammation/CRP Evaluation (PRINCE)[8], Aggrastat- to- Zocor (A to Z)[9] and Justification for the Use of Statins in Primary Prevention: an Intervention Trial diagnosis Rosuvastatin (JUPITER)[10] indicate that cardiovascular benefits are more apparent when systemic inflammation (as evidenced by hsCRP reduction) is reduced in addition to intensive low-density lipoprotein cholesterol (LDL-C) lowering. The A to Z trial evaluate that the best clinical outcomes occurred when the hsCRP levels were lowered below 2 mg/l in addition to LDL-C lowering to < 70 mg/dl. An imbalance between pro- and anti-inflammatory factors contributes to the atherosclerotic process. Inflammatory processes have an effect on the integrity of the fibrous cap in atherosclerotic plaque. Pro-inflammatory processes involving innate and adaptive immune mechanisms weaken the fibrous cap, causing a predisposition towards its rupture.[2] Interferon-γ (IFN-γ) elaborated by activated T cells suppresses collagen production by smooth muscles cells of the arterial wall.

This is coupled with enhanced collagen degradation in the fibrous cap mediated by the matrix metalloproteinase enzymes (MMP-1, MMP-8, MMP-13) synthesized by activated macrophages. These processes enhance the friability of the fibrous cap.[11] In primary prevention, CRP confers additional prognostic value at all levels of Framingham risk and at all levels of the metabolic syndrome and blood pressure.[1012,13] In head-to-head comparisons with LDL cholesterol, CRP was found to be the stronger predictor of incident cardiovascular events.[13]

Even, CRP predicts not only incident myocardial infarction and cardiovascular death, but also risk of ischemic stroke, sudden cardiac death, incident peripheral artery disease and restenosis after percutaneous coronary intervention.[14-17]

This robust association with future cardiovascular events has provided an analytic opportunity for CRP in clinical use. CRP is an appropriate marker because it has a long half-life, its levels remain stable over time without exhibiting circadian variability and fasting blood samples are not required.

Currently, CRP levels <1 mg/L, 1 to 3 mg/L, and >3 mg/L are used to denote low-, intermediate-, and high cardiovascular risk groups.[18]

MATERIALS & METHODS

The present study was Operated at Department of Biochemistry, G.C.R.G. Medical College, in which 200 patients of Ischemic Heart Disease (study group) primarily diagnosed by clinical examination and biochemical investigations admitted to the intensive cardiac care Unit (ICCU) and 50 apparently healthy subjects (control group) were included. Informed consent was obtained from all participants. Fasting blood samples were collected and laboratory investigations like hs-CRP (immunoturbidimetric method), LDL-C (direct method), HDL-C (direct method), total cholesterol (CHOD-PAP enzymatic method), triglyceride (GPO-PAP enzymatic method), plasma glucose (GOD-POD enzymatic method) and Ck-MB (Immunoinhibition UV Kinetic method) were carried out on fully auto analyzer- Miura, A-1005 (ISE-Italy) at NABL (ISO 15189:2007) accredited, Clinical Biochemistry Section, Laboratory services.

Explanatory statistics are shown as mean ± standard deviation. Mean levels of all parameters of case and control groups were compared by unpaired t-test. Normal distribution was tested and data was found to follow normal distribution. *p* value less than 0.05 was considered significant.

Table 1: Comparison of Control & Study Group

Parameters	Biological Reference Interval	Control group (n=100)			Study group (n=200)			Significance (two tailed p value)
		Mini.	Maxi.	Mean ± SD	Mini.	Maxi.	Mean ± SD	
hsCRP mg/L	0.3- 8 mg/L	0.7	8.0	5.99 ± 3.09	2	260	47.3 ± 64.9	t=4.59 **p < 0.0001
LDL-C mg/dl	80-130 mg/dl	39	230	109 ± 43.03	40	431	132.3 ± 55.9	t=2.57 *p=0.0110

Note: * p < 0.05 = Significant, **p < 0.01 = Highly significant, p >0.0 = Not significant

Table 2: hs-CRP levels in case & control group

hs-CRP	Study	Control	Total
>8	170	0	170
<8	30	100	130
Total	200	100	300

The specificity of the hs-CRP is (100%) and the sensitivity is (85%)

Table 3: LDL-C level in study& control group

LDL-C mg/dl	Study	Control	Total
>130	87	37	124
<130	113	63	176
Total	200	100	300

The specificity of LDL-C is (66%) and sensitivity is (44%).

RESULTS

Table (1) shows the comparison of hs-CRP and LDL-C in the study group and control group.

The mean ages of the groups were not significantly different. It was observed that out of levels of hs-CRP were significantly higher (p < 0.0001) in study group as compare to control group, while the levels of LDL-C were also significantly higher in study group in comparison to control group (p< 0.05)

Table (2) and (3) shows the comparison between the sensitivity and specificity of hs-CRP and LDL-C. It was found that hs-CRP had 85% sensitivity and 100% specificity whereas LDL-C had only 44% sensitivity and 66% specificity. The results showed that the hs-CRP was more sensitive & specific as compare to LDL-C.

DISCUSSION

In the f present study, Mean age in the study group was 60 ±10 years and that in control group was 50 ± 10 years. Total 90% patients were above 40 years of age, the rest of 10% belonged to younger age group. The age phenomenon of Ischemic Heart Disease demonstrate that the risk of IHD higher in older age as compare to young age. In a study conducted by Nader Rifai in 1997 in Boston the mean age in cases was 50.9±9.[19,20] In a study which is conducted by Sunil S. Patani in 2013 , Mean age in the study group was 57.8 ±12.58 years and that in control group was 46.3±12.17 years.[21]

In a study conducted by Ridker, P.M. (1998), distribution of hs-CRP among apparently healthy American men and women was 0.01 – 0.07 mg/dl - low, 0.07 – 0.11 mg/dl - mild, 0.12 -0.19 mg/dl- moderate,0.20-0.38 mg/dl -high,0.38-1.50 mg/dl-highest.[14]

In a present study the levels of hs-CRP in control group were in between 0.3 to 8 mg/L. The mean value in control group was 5.99 mg/L. In study group 98% patients had the level of hs-CRP more than 8 mg/L which demonstrated increase in hs-CRP level in patients of IHD.

In a study conducted by Sunil S. Patani in 2013; the levels of hs-CRP in control group were in between 0.3 to 8 mg/L. The mean value in control group was 4.99 mg/L. In study group 97% patients had the level of hs-CRP more than 8 mg/L which indicate marked increase in hs-CRP level in patients of IHD.[21] In a case control study conducted by Paul M. Ridker et al. the mean CRP in CHD cases was significantly higher 6.45 mg/L as compared to controls 3.75 mg/L (p<0.0001).[22]

In a study conducted by Nader Rifia et al. men with angiographically documented CHD, it was demonstrated that there was a highly significant (p<0.0001) difference in hs-CRP values between cases and controls.[23]

CONCLUSION

The study demonstrated that the half of the IHD patients with normal LDL-C levels had significantly elevated levels of hs-CRP. Furthermore, in regard to sensitivity and specificity hs-CRP is far better predictor of IHD than LDL-C. Therefore, hs-CRP should be included in the standard protocol as a better and single predictor of IHD than conventional lipid profile which will improve the physician's ability for the early and better prediction of future occurrence of ischemic heart disease in patients.

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