Original Article

Correlation of high sensitivity C-reactive protein and low density lipoprotein cholesterol level in healthy south Indian population

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Abstract

Introduction: Inflammation plays a key role in pathogenesis of atherosclerosis. Estimation of high sensitivity C-reactive protein (hs-CRP), an inflammatory marker improves in identification of "at risk" individuals for cardiovascular diseases (CVD). Few data are available regarding distribution of hs-CRP levels in South Indian population. **Aim:** To correlate the distribution of plasma levels of hs-CRP with low density lipoprotein (LDL) cholesterol in healthy subjects. **Methods:** Hs-CRP and LDL levels were estimated in healthy South Indians (Total = 990, 747 males and 243 females) above 18 years of age. Based on hs-CRP levels individuals were categorized: low risk < 1 mg/L, average risk- 1 to 3 mg/L, high risk >3 mg/L and then correlated with LDL cholesterol. **Results:** Women had higher mean hs-CRP level and they were found to be at "high risk" category than men (56% Vs 39.1%, chi-square-21.9, p <0.0001). More than one third (36.6%) of men and half (53.3%) of women with normal LDL levels were in "high risk" hs-CRP category. Hs-CRP might be useful to identify at-risk individuals but with normal LDL levels, especially in women (rho =0.145, p<0.024) when compared to men (rho =0.122, p<0.058). **Conclusions:** A significant subset of South Indians with normal LDL-cholesterol levels had elevated hs-CRP. Hence, screening for hs-CRP may improve identification of high risk individuals.
Keywords: High sensitivity C-reactive protein, Low Density Lipoprotein cholesterol and South Indians.

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INTRODUCTION

Coronary Artery Disease (CAD) is the leading cause of morbidity and mortality in developing countries. Conventional risk factors have limitations in identifying individuals "at risk" for CAD. Ridker *et al*. observed 77% and 46% of CV events in persons with moderately elevated and normal levels of low-density lipoprotein (LDL) cholesterol respectively[1]. Also, it has been reported that about half of first cardiovascular events occurred in healthy postmenopausal women without any traditional risk factors[2,3]. Hence several research works have been attempted in identification of novel risk factors for atherosclerosis and cardiovascular diseases (CVD). Atherosclerosis was considered as a passive process of cholesterol deposition in the arteries and later it has been identified as an active inflammatory disease[4]. Inflammation is found to have key role in the development of the various stages of atherosclerosis, from onset and progression of atheroma to plaque instability with erosion and restenosis following angioplasty[5-7]. Various plasma markers of inflammation have been studied as potential parameter to predict the risk of future coronary events. Among them, high sensitivity C-reactive protein (hs-CRP) has been studied most extensively and it was found to be not only as an

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inflammatory marker but also but also plays an active role in atheroma formation[8,9]. Prospective studies in apparently healthy men and women have shown hs-CRP has been useful in predicting future CVDs independent of other conventional risk factors. Also, it has been shown as a stronger predictor than LDL cholesterol and provide an incremental information in identification of individuals "at risk" for CV events and sudden cardiac death[1,10,11]. In patients with Unstable Angina (UA) where cardiac enzymes are not elevated, hs - CRP levels at admission help predicting subsequent CV events[12]. Similarly, it provides added prognostic value on future risks in healthy persons with metabolic syndrome of various levels of severity[13]. In middle-aged healthy women, elevated hs - CRP levels predict the development of type 2 diabetes mellitus[14]. Data regarding the distribution of hs-CRP levels in healthy South Indian population are very minimal. Hence, the objective of the current study is to assess the distribution of hs-CRP level and correlate with LDL cholesterol in healthy South Indians.

MATERIAL AND METHODS

A retrospective study was done from medical records of the 990 healthy subjects who visited the outpatient department for routine health check up at Chettinad Hospital and Research Institute, Chennai between June 2013 to May 2014. Individuals above 18 years of age in both sexes were included in the study and their plasma hs-CRP, LDL cholesterol levels were correlated. Subjects with diabetes (DM), hypertension (HT), CAD and those who were on aspirin, statins or hormone replacement therapy were excluded from the study. Additionally, patients with chronic infectious and inflammatory disorders (e.g. tuberculosis, rheumatoid arthritis and systemic lupus erythematosus), autoimmune diseases and malignancies were also excluded. Based on plasma hs-CRP levels, individuals were categorized as *low* (< 1mg/L), *average* (1 to 3 mg/L) and *high risk* (>3 mg/L) as recommended by the American Heart Association and Centers for Disease Control and Prevention (AHA/CDC) guidelines[15]. LDL cholesterol is considered as *optimal or near optimal* (below 130 mg/dl), *borderline high* (130 to 159 mg/dl) and *high* (≥160 mg/dl) according to the Framingham's risk score[16] and National Cholesterol Education Program (NCEP) Expert Panel / Adult Treatment Panel III (ATP III)[17].

Statistical Analysis

All the statistical analysis were done by using SPSS software (version 16.0). Chi square test was used to compare proportions and T-test / Mann Whitney test was used to compare the difference in distribution of Hs-CRP and LDL between males and females. Spearman rank correlation coefficient was calculated to assess the correlation between LDL and hs-CRP.

RESULTS

A total of 990 individuals comprised of 747 (75.5%) males and 243 (24.5%) females with a higher mean age for females (50.4 ± 10) than males (46.6± 12.6). Mean hs-CRP level in females was higher than males (5.06 Vs 4.4, p<0.0001) whereas no difference was observed in LDL level among them (126 Vs 128, p=0.540) [Table 1]. Low, average and high risk category of Hs-CRP for males were 11.9%, 49% and 39.1% and for females were 7%, 37% and 56% respectively. Females were found to be at 'high risk' than males (chi-square-21.9, p <0.0001)[Table 2]. Optimal, borderline high and high level of LDL category for males were 50.5%, 30.5% and 19% and for females 55.6%, 23% and 21.4% respectively. No significant difference was found in LDL level among them (chi-square-5.0, p value- 0.081) [Table 2]. Further, hs-CRP levels were correlated with LDL to find the association among them. It was found that 47.1 and 41% of overall population, 50.1% and 36.61% of males and 38.5% and 53.3% of females with optimal LDL had average and high risk hs-CRP levels respectively. Spearman rank correlation coefficient for overall (rho = 0.112, p<0.0001), male (rho = 0.122, p = 0.058) and females (rho= 0.145, p = 0.024)

Table 1: Distribution of HS-CRP and LDL in study population

Parameter	Group	Minimum	Maximum	Mean	Standard Deviation	Statistical distribution	*P* value
HS-CRP (mg/l)	Overall	.10	91.75	4.5663	7.20	70842#	<0.0001
	Male	.10	91.75	4.4	7.87		
	Female	.10	20.80	5.06	4.57		
LDL (mg/dl)	Overall	17	274	127.95	38.36	0.613*	0.540
	Male	17	274	128.38	37.63		
	Female	17	226	126.64	40.57		

HS-CRP- high sensitivity C Reactive Protein, LDL- low density lipoprotein, #Mann Whitney U statistic was used as the outcome variable (HS-CRP values) were non-normally distributed *t-statistic was used as the outcome variable (LDL values) was normally distributed

Table 2: Distribution of HS- CRP and LDL levels among study population

Risk categorization of study population based on hs- CRP levels				
Risk category (hs-CRP level)*	**Overall**	**Male**	**Female**	x^2
Low risk (<1 mg/L)	106 (10.7%)	89 (11.9%)	17 (7%)	21.916, p<0.0001
Average risk (1-3 mg/L)	456 (46.1%)	366 (49%)	90 (37%)	
High risk (>3 mg/L)	428 (43.2%)	292 (39.1%)	136 (56%)	
Distribution of LDL levels among study population				
Risk categories(LDL level)#	**Overall**	**Male**	**Female**	x^2
Optimal (<130 mg/dl)	512 (51.7%)	377 (50.5%)	135 (55.6%)	5.025, p = 0.081
Borderline high (130-159/dl)	284 (28.7%)	228 (30.5%)	56 (23%)	
High (≥160 mg/dl)	194 (19.6%)	142 (19%)	52 (21.4%)	

*Cut-off values of hs-CRP for based on the American Heart Association and Centers for Disease Control and Prevention recommendation.
#LDL levels were classified based on Adult Treatment Panel III, Statistical analysis was done by Chi square test and p value < 0.05 is considered to be significant

Table 3: Correlation of HS- CRP and LDL levels among study population

Correlation between LDL levels and HS-CRP levels among study participants				
Study Participants	**LDL level**	**Hs-CRP<1mg/L**	**Hs-CRP 1 to 3mg/L**	**Hs-CRP>3mg/L**
Overall*	< 130 mg/dl	61 (11.9%)	241 (47.1%)	210 (41%)
	130 to 159 mg/dl	28 (9.9%)	131 (46.1%)	125 (44%)
	≥160 mg/dl	17 (8.8%)	84 (43.3%)	93 (47.9%)
Male#	< 130 mg/dl	50 (13.3%)	189 (50.1%)	138 (36.6%)
	130 to 159 mg/dl	26 (11.4%)	110 (48.2%)	92 (40.4%)
	≥160 mg/dl	13 (9.2%)	67 (47.2%)	62 (43.7%)
Female$	< 130 mg/dl	11 (8.1%)	52 (38.5%)	72 (53.3%)
	130 to 159 mg/dl	2 (3.6%)	21 (37.5%)	33 (58.9%)
	≥160 mg/dl	4 (7.7%)	17 (32.7%)	31 (59.6%)

Spearman rank correlation coefficient - rho = 0.112, p<0.0001(overall), rho = 0.122, p = 0.058(male), rho= 0.145, p = 0.024 (female)

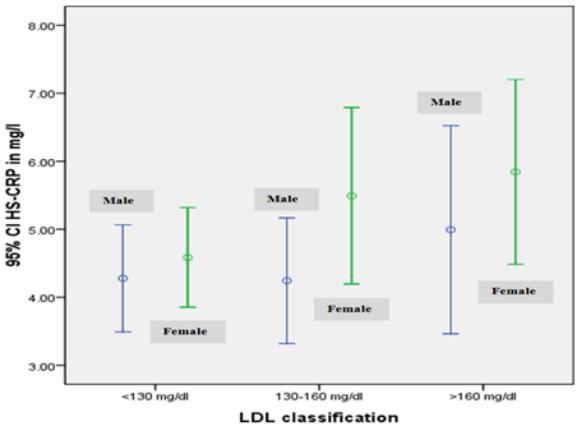

Figure 1: Error bar graph showing association distribution of HS-CRP levels among different LDL risk groups
*95% confidence interval of mean Hs-CRP levels are presented for each LDL risk category

DISCUSSION

Atherosclerotic cardiovascular diseases are the major cause for increased mortality rate globally. Assessment of conventional risk factors for CAD like age, sex, LDL Cholesterol, diabetes, hypertension, smoking, family history and obesity have been used for decades in identifying "at risk" individuals. However, several documented CAD patients were found to have none of these risk factors and identification of other novel risk factors has become more essential in the current era of preventive cardiology. In western population, Hs-CRP has been evaluated as a predictive tool for CV event in healthy as well as established CAD individuals[1,3,11-13]. Hs-CRP is a non-specific inflammatory marker having long half-life (19 hours), relative stability without significant diurnal variation. Trace amount of CRP is normally detectable in healthy persons and highly elevated in autoimmune diseases, infections and malignancies. CRP levels that predict cardiovascular risk may be as low as 1mg/L which cannot be detected by route methods. Hence, estimation of standardized high sensitivity assay of CRP (hs-CRP) was done[15]. As per the

National Health and Nutrition Examination Survey (NHANES), mean hs-CRP level in American adults was 4.3±7.7 mg/L[18]. In the current study, we found higher mean hs-CRP level (4.5 ± 7.2 mg/L) in healthy south Indians. However, from this observation alone, it cannot be presumed that Indians are at a higher risk for CVDs due to the existence of inter ethnic variations[18]. Further, Kamath *et al* found a higher mean hs CRP among Indians in his meta-analysis which is in agreement with our observations. However, majority of his study controls were North Indians with smaller group of population[19]. Similarly, Indians living in other countries were found to have higher baseline hs CRP compared to their respective native ethnic population: higher than Europeans in United Kingdom[20], Caucasians in the United States[21] and Chinese as well as Malays in Singapore[22] On classifying our study population according to the AHA/CDC guidelines on clinical application of hs-CRP, we observed about 88% of men and more than 90% of women have been found to have average to high risk CRP levels. More women were found to be at 'high risk' category than men based on the hs-CRP level (56% Vs 39%, chi-square 21.9, $p<0.0001$). Even mean hs-CRP level was significantly higher in women than men (5.06 Vs 4.4, $p<0.0001$) in the present study which is in concordance with finding in NHANES survey[18]. Mahajan *et al.*[23] and Rao *et al*.[24] also observed similar findings among North Indian population. Based on this observation, it is difficult to conclude that Indian females are at a higher risk than males for future CV events as there are no large prospective follow up studies available in Indian population. The probable reason for increased Hs-CRP level among Indian female could be due to higher mean age, because Hs-CRP level increases with age[18]. Moreover, it has been clearly shown that women especially premenopausal subsets are less prone to develop CAD than their counterpart males[16]. In women's Health Study, hs-CRP and LDL levels of 27,939 healthy subjects were compared and followed for 8 years for CV events. Occurrence of CV events were more common in women with higher hs-CRP (2.10 and 4.1 mg/L) than lower level (< 0.49 mg/L) and concluded that hs-CRP was found to be a stronger predictor for CV events than LDL[1]. Another study done by Ridker *et al*. in a population of 28263 healthy postmenopausal women have reported that measurement of hs-CRP in addition to lipid levels improved the identification of women at risk for CV events[3]. In Physician's Health Study, healthy men were followed for a period of eight years and observed men with highest CRP levels had higher MI ischemic stroke[11]. However, these studies were done in western population. NCEP/ATP III guidelines recommend statins therapy for primary prevention in individuals with high LDL cholesterol (>160 mg/dl)[17]. However, JUPITER study group reported that statin therapy decreases the CV events in patients with normal LDL and elevated hs CRP[25]. In the current study, it was found that a significant proportion of individuals with normal LDL cholesterol had elevated hs-CRP levels. Hence, screening for lipids alone failed to identify a subset of individuals at-risk for CV events. Our study has limitations of single centre study and follow-up for CV events was not done. Hs CRP may be a novel predictor for CAD and further studies are required with a larger population to define normal range of hs-CRP and new cut-off levels for Indian population.

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