High Sensitive C Reactive Protein and the Calculated Framingham Coronary Heart Disease Risk Score in a Selected Population of Sri Lanka

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Abstract:

Recently, the inflammatory marker, high sensitivity C-reactive protein (hsCRP) has attracted clinical attention as a novel risk factor for Coronary Heart Disease (CHD) due to the immerging relationship between inflammation and atheroma.

Objective:

To assess the correlation between hsCRP and the risk of CHD derived from Framingham Coronary Heart Risk Score (FCRS) in a selected population of Sri Lanka.

Methods:

A descriptive cross sectional study was conducted with 115 middle aged (40-65years) individuals of University of Sri Jayewardenepura, Sri Lanka. Their baseline characteristics such as age, gender, smoking status, body mass index (BMI), blood pressure levels, cholesterol levels and status of diabetes were obtained and FCRS was calculated. Levels of hsCRP were measured by using photometric technique.

Results:

The median hsCRP level of the participants was 1.10mg/L. 54.3% of the participants had high levels (>1mg/L) of hsCRP. Among overweight individuals 64.8% had high levels of hsCRP. Other traditional risk factors measured did not showed any significant correlation with hsCRP. Also, no significant correlation was found between hsCRP and FCRS.

Conclusions:

The median hsCRP value for Sri Lankan population was lower than that of the Western population. The findings of the study indicated that hsCRP could not be used as a single indicator to predict the risk of Cardio Vascular Diseases (CVD) instead of FCRS and other traditional risk factors.

Key words:

Cardiovascular disease, High sensitive C-reactive protein, Framingham Coronary Heart Disease Risk Score.

Introduction:

Coronary Heart Disease (CHD) has been reported as the second most common cause of death globally. Although the burden of CHD has been reduced in several developed countries, its prevalence rate in Sri Lanka has not declined [1,2]. The traditional risk factors of CHD are age, gender, hypertension, hyperlipidemia, smoking, diabetes mellitus, family history and obesity [3,4]. All CHD cannot be explained by using those traditional risk factors, though they play a major role in the development of most of the CHD[1].Recently inflammation has been identified as an important factor in atherosclerosis and high sensitivity C- reactive protein (hs-CRP) has attracted clinical attention as a novel risk factor for CHD [1, 5, 6]. According to available data, it has become the most effective marker and predictor, comparing to new biomarkers in determining CHD risk[4].

However, the correlation between hs-CRP as a risk factor for CHD are mostly restricted to studies done on Western population [2,7]. Framingham Coronary Heart Risk Score (FCRS) is a multiple risk prediction model and is used to predict a person's future risk of CHD. FCRS is calculated by using traditional risk factors of CHD such as age, lipid status (total cholesterol and HDL cholesterol), body mass index (BMI), current smoking status, diastolic pressure and systolic pressure[8,9]. Since the middle aged population (40-65 years) is the most vulnerable group for future CHD, the prediction of cardiac risk among them is important [7]. Knowledge on novel and traditional risk factors is important in the effective prevention of CHD. This drew the attention towards new risk factors which could account for unexplained CHD risks. It is not justifiable to apply those finding to Sri Lankan population since no studies have been carried out in Sri Lanka to investigate the association between the hs-CRP and CHD until now. Hence this study was carried out to rationalize the impact of serum hs-CRP levels as a predictor on future development of CHD in a selected population of Sri Lanka by using FCRS.

Methods:

After obtaining approval from the ethical review committee of the University of Sri Jayewardenepura, Sri Lanka, a descriptive cross sectional study was conducted from August 2012 to August 2013 . Apparently healthy middle aged (40-65years) individuals of both gender were included in the study after obtaining their written informed consent. Among 115 participants 105 individuals were recruited considering exclusions due to following reasons: confirmed CHD such as Myocardial Infarction (MI), angina, congestive heart failure, stroke, coronary artery bypass surgery, angioplasty and the individuals with inflammatory conditions, infections, fever, eczema, trauma, rheumatic disease with hsCRP levels >10mg/L.Blood (1mL) was collected from fasting participants for glucose, lipid and hsCRP analysis. Participants were at overnight fasting (10-12 hours) state at the time of blood collection. Glucose-oxidase method was used to determine the plasma glucose levels and diabetes was defined by fasting blood glucose levels (≥110mg/dL). Enzymatic methods were used to determine total cholesterol and high density lipoprotein (HDL). Friedewald formula was used to estimate the low density lipoprotein (LDL) cholesterol levels. Serum cholesterol level of 200mg/dl or higher was considered as the cutoff level for hypercholesterolemia. Serum specimens collected were stored at -20°C until they were used for hs-CRP assay using particle enhanced immunoturbidimetric method[10]. hsCRP>1mg/Lwas considered as high[2].

A sphygmomanometer was applied at the right upper arm to measure the Blood Pressure (BP)of the participants after 5 minutes of rest. The participants were considered as hypertensive if BP level was ≥ 140/90 mm Hg. BMI (Kg/m^2) was calculated by obtaining the height and weight of consented participants. When the subjects had BMI of ≥ 25 Kg/m^2, they were considered as obese. Information on smoking habits, age and gender was obtained using a standard questionnaire. Gender, age, smoking status, diabetes status, systolic blood pressure, diastolic blood pressure, total cholesterol levels and HDL levels were used to calculate the FCRS according to Framingham Heart Study[11]. For Sri Lankans multiplying the FCRS by a correction factor 1.4 has been suggested[12]. Base line characteristics from participants were categorized into low and high groups. hsCRP>1mg/L, FCRS>10%, blood pressure > 140/90mmHg, Total cholesterol >200mg/dL, LDL > 150mg/dL, HDL >40mg/dl, diabetes >110mg/dL, BMI > 25Kg/m^2 were taken as high levels (Table 1). SPSS version 21.0 was used for the data analysis. Descriptive statistical methods were used to describe and present data. Chi square test was used to find out the association between categorical variables. $P < 0.05$ was considered significant.

Results:

Among 105 participants the median hsCRP level was 1.10mg/L. The mean age, BMI, Systolic Blood pressure, Diastolic Blood pressure, Blood Glucose, Cholesterol, HDL and LDL of patients were 50.09 (49.18 - 50.99), 25.35 (24.61-26.08), 129.72 (126.23-133.2), 84.78 (82.59-86.96), 104.57 (95.28-113.85), 189.53 (182.68-196.37), 46.55 (44.86-48.23) and122.42 (115.76-129.07) respectively. There is significant association between the BMI of High and low CRP group (P-value <0.05). The baseline characteristics of the subjects by hs-CRP were shown in Table 1.

Characteristic	Total (n=105) Mean (95%CI)	High CRP (n=57) Mean(95%CI)	Low CRP (n=48) Mean(95%CI)	P-Value
Age (Years)	50.09 (49.18 - 50.99)	50.14 (48.89-51.38)	50.02 (48.68-51.35)	0.89
BMI (Kg/m^2)	25.35 (24.61-26.08)	26.1 (25.09-27.22)	24.3 (23.46-25.31)	0.01*
Systolic blood pressure (mmHg)	129.72 (126.23-133.2)	130.86 (125.66-136.05)	128.38 (123.89-132.87)	0.48
Diastolic blood pressure (mmHg)	84.78 (82.59-86.96)	85.16 (82.09-88.22)	84.33 (81.20-87.45)	0.71
Blood Glucose levels (mg/dL)	104.57 (95.28-113.85)	109.42 (95.2-123.63)	98.81 (87.59-110.03)	0.26
Total cholesterol (mg/dL)	189.53 (182.68-196.37)	190.53 (181.02-200.03)	188.35 (178.41-198.28)	0.75
HDL (mg/dL)	46.55 (44.86-48.23)	45.86 (43.33-48.38)	47.38 (45.19-49.56)	0.38
LDL (mg/dL)	122.42 (115.76-129.07)	124.07 (114.64-133.49)	120.46 (111.09-129.83)	0.59

Table 1: Baseline characteristics by high and low hs-CRP
*Independent sample t test * CI- Confidence Interval

hs-CRP(highest vs lowest) for development of CHD among major clinical sub groups defined by the absence or presence of other cardiovascular risk factors are summarized in Table 2. The risk factors considered in the current study were BMI, diabetes, hypertension, smoking, hypercholesterolemia, high LDL, and low HDL. According to the results 35(64.8%) overweight individuals had high hsCRP levels. A proportion of normal weight individuals 22(43.1%) also had high hsCRP levels showing a statistically significant difference. Table 2 showed that 10(62.5%) of participants with diabetes had high hsCRPlevels, and 47(52.8%) participants with no diabetes also had high hsCRP levels. The difference shown was not statistically significant. According to the Table 2, 13(52%) hypertensive had high hsCRP levels and 44(55%) normotensives also had high hsCRP levels which was not significant. The results further revealed that 5(41.7%) smokers and 52(55.9%)nonsmokers had high hsCRP

levels with no significant correlation. An insignificant association was observed between hypercholesterolaemic participants 22(61.1%) and participants with normal cholesterol levels despite their high hsCRP levels. Other lipid parameters (HDL and LDL) also showed a negative correlation among the groups tested.

	hs CRP levels			
	High >1mg/dL (%)	Low < 1mg/dL (%)	Chi Square value	p-value
Diabetes Present	10(62.5)	6(37.5)	0.513	df=1 P>0.05
Absent	47(52.8)	42 (47.2)		
Hypertension Present	13 (52.0)	12(48.0)	0.069	df=1 P>0.05
Absent	44 (55.0)	36(45.0)		
Lipid status				
a)Hypercholesterolemia Present	22(61.1)	14(38.9)	1.028	df=1 P>0.05
Absent	35(50.7)	34(49.3)		
b) LDL High	14(56.0)	11(44.0)	0.039	df=1 P>0.05
Normal	43(53.8)	37(46.3)		
c) HDL Low	16(57.1)	12(42.9)	0.126	df=1 P>0.05
Normal	41(53.2)	36(46.8)		
Current smoking Yes	5(41.7)	7(58.3)	0.869	df=1 P>0.05
No	52(55.9)	41(44.1)		
Obesity Present	35(64.8)	19(35.2)	4.967	df=1 P<0.05
Absent	22(43.1)	29(56.9)		

Table 2: Association between hsCRP levels and traditional cardiac risk factors

*df= degree of freedom
*the values given in the brackets are the percentages
*Chi square > 3.84 significant

Table 3 shows the association between calculated FCRS and the level of hsCRP. High risk category was defined when FCRS is more than 10%. It was observed that there was a non-significant association (P>0.05) between hsCRP levels and FCRS.

FCRS	Level of hsCRP	
	High >1mg/dl	Low < 1mg/dl
High risk	23 (40.4%)	23 (47.9%)
Low risk	34 (59.6%)	25 (52.1%)
Total	57 (100.0%)	48 (100.0%)

Table 3: Association between FCRS and the level of hsCRP

Chi square 1.028, df=1, P>0.05
*N= number of participants
*The values given in the brackets are the percentages

Discussion:

There has been a considerable ongoing debate regarding the usefulness of the novel risk factor hs-CRP as a potential risk predictor of CHD events and its potential casual role in the atherogenic process[10]. The assumption of this study was to obtain elevated levels of inflammatory marker hs-CRP in the participants at high risk of CHD. In the present analysis the median hsCRP value observed (1.10mg/L) was lower than that of Western populations (median approximately 1.5 to 2.0 mg/L), but higher than the level of Japanese population (0.43mg/L)[2]. Other cross sectional studies had also shown similar results predicting that Asian subjects had lower hsCRP levels compared to Western subjects[2,9,13].Western studies categorized hsCRP levels as low (<1mg/L),intermediate (1-3mg/L) and high (>3mg/L)[7,14]. It has been reported that the cutoff value of hsCRP level >1mg/L is likely to be high risk category of the CHD among Asian population[2,13]. In the present study the criteria applicable for Asian population was used. In the cross sectional study, an independent association was obtained between the effects of hs-CRP on the risk of future coronary events and the other cardiovascular risk factors such as hypertension, diabetes, or smoking habits[2]. This is in contrast with some cross sectional studies which had shown a significant association between hsCRP levels and other traditional risk factors of cardiac disease[4,9,13]. In the current study most of the baseline characteristics were

obtained by direct measurements. Diabetes status and lipid levels were determined by blood testing. Some studies have obtained the information on some of the risk factors by a questionnaire rather than direct measurements. Self-reporting could lead to misclassification of risk factor status[7,14]. A strong association was found between BMI and high hsCRP levels from current study (P<0.05). Similar findings were reported in a study, where among other risk factors the highest association of hsCRP was seen with obesity[9,10,13]. In current study no relationship was observed between FCRS and hs-CRP. Consistent with this observation, a positive correlation between FCRS and hs-CRP could not established by several large studies[15,16]. The FCRS is frequently used as a non-invasive screening tool to measure CHD risk in clinical practice and public health research. However the predictive ability of the FCRS varies between populations, ethnic groups and socio-economic status[15]. This could be a possible explanation for this discrepancy between hs-CRP levels and the FCRS in our study. Several limitations of current study should be discussed. The major limitation was the small sample size of 115 individuals. Previous studies had used several thousands of people[2,9,17]. Therefore, results obtained with this sample size may vary, if higher sample size would be used. Second limitation is the cutoff point of hsCRP. There is an ethnic variation in hsCRP distribution[9,16].There are no studies to demonstrate the cut off points of hsCRP for Sri Lankan population. Therefore, the true cut-off point for detection of high risk subjects may be higher or lower than the values used in this study. It has been stated that, hsCRP concentrations can be affected by diurnal variation and infection[18].Only few smoking individuals were identified because smoking status was obtained by questionnaire even the smokers would have failed to give true response. Given that these limitations might have underestimated the association between hsCRP and FCRS and traditional risk factors. However the present study has a strength in that this is the first study in Sri Lanka to examine the casual relationship between novel inflammatory marker hs-CRP and CHD risk.

Conclusions:

The present study concluded that the median hsCRP value for a population from Sri Lanka was lower than that of the Western population. In current study serum hsCRP levels did not show any significant relationship with FCRS as well as with other cardiovascular disease risk factors, other than overweight where the highest association was obtained. However the present study revealed that hsCRP cannot be used as a single indicator to predict the risk of cardiovascular disease on behalf of FCRS and other traditional risk factors.

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