Original Article

Correlations Between the Level of High-Sensitivity C-Reactive Protein and Cardiovascular Risk Factors in Korean Adults with Cardiovascular Disease or Diabetes Mellitus: The CALLISTO Study

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Aim: We assessed the relationship between the level of high-sensitivity C-reactive protein (hsCRP) and cardiovascular risk factors in Korean adults.

Methods: We reviewed 1,561 patients with cardiovascular disease or diabetes mellitus with hsCRP levels measured within the past year. Four cardiovascular risk groups were determined: low ($<10\%$, 0-1 risk), moderate ($<10\%$, >2 risk), high (10-20%) and very high ($>20\%$) risk, according to the number of risk factors and the Framingham/NCEP ATP Ⅲ risk score. The correlations between the hsCRP level and cardiovascular risk factors (age, smoking, hypertension, lipid profiles and familial history of premature coronary heart disease) were investigated.

Results: The mean and median hsCRP (mg/L) levels were 1.32 ± 9.69 and 0.29 (range: 0.01-7.48), respectively. Men had a higher median level of hsCRP than women ($p<0.001$). The levels of hs CRP significantly increased from the low to the very high risk group (0.15, 0.23, 0.27 and 0.47, respectively) and were significantly correlated with age, the level of glycosylated hemoglobin, body mass index (BMI), the level of high-density lipoprotein cholesterol (HDL-C), the low-density lipoprotein cholesterol (LDL-C)/HDL-C ratio, the LDL-C/total cholesterol (TC) ratio, the HDL-C/TC ratio, the HDL-C/triglyceride (TG) ratio and the TC/TG ratio. Neither smoking, the LDL-C level nor the TG level affected the hsCRP level. In a multivariate regression analysis, age, the HDL-C level, the LDL-C/TC ratio and BMI were found to be independently correlated with the hsCRP level.

Conclusions: There is a significant relationship between the degree of cardiovascular risk and the hsCRP level in Korean adults with cardiovascular disease or diabetes mellitus. Assessing the hsCRP levels may thus provide additive value in predicting cardiovascular risks.

Introduction

There are various risk factors for cardiovascular disease, including age, smoking, obesity, insulin resistance, diabetes mellitus, hyperlipidemia and hypertension. Among these risk factors, hyperlipidemia is known to be a major risk factor for cardiovascular disease, and lowering the levels of low-density lipoprotein cholesterol (LDL-C) is the primary focus of lipid modification for atherosclerosis prevention and treatment[1, 2]. However, patients may present with cardiovascular events despite having an LDL-C level that falls well within guideline-recommended targets[3]. Therefore, in an attempt to predict cardiovascular events, many investigators have focused on novel risk factors that reflect different aspects of atherogenesis, with hopes that identifying new biomarkers will provide alternative or adjunct methods to assessing the LDL-C level for predicting cardiovascular events.

Recent research has shown that chronic inflammation is associated with cardiovascular risk factors and plays a key role in the progression of atherosclerotic coronary heart disease[4]. The level of high-sensitivity C-reactive protein (hsCRP) serves as a chronic inflammatory marker and has been shown to be a predictor of cardiovascular events, regardless of the LDL-C level, in several large studies[5-7]. Moreover, the CRP level has previously been demonstrated to be a stronger predictor of future cardiovascular events than the LDL-C level[8]. The associations between the hsCRP level and major cardiovascular risk factors have previously been studied in Korean populations; however, these studies were small sample, single-center studies[9, 10].

In the present large and multicenter study, we investigated the associations between the hsCRP level and various cardiovascular risk factors, including lipid profiles, in Korean adults and identified the utility of the hsCRP level as a marker of cardiovascular disease.

Methods

Study Population

The CALLISTO (CorrelAtion of pLasma hsCRP concentrations and cardiovascuLar rISk in Korean

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populaTiOn) study (NCT 00819273) is a nationwide multicenter, cross-sectional, observational study that took place between April 2008 and July 2009. The study protocol was approved by the Institutional Review Boards of each participating hospital. The study population consisted of 1,561 consecutive patients over 18 years of age with diabetes mellitus or cardiovascular diseases, such as hypertension or coronary heart disease (CHD), whose hsCRP level had been tested at least once during the past year. The diagnostic criteria for CHD included classic angina symptoms or positive results on an exercise treadmill test. Acute coronary syndrome was not included in the diagnostic criteria.

The criteria for exclusion included the use of statins or lipid-lowering agents, such as fibrates, niacin or bile acid sequestrants, during the previous quarter of the year before measuring the hsCRP level, the presence of an active inflammatory disease at the time of measuring the hsCRP level, treatment with hormone replacement therapy, the use of immune suppressants, a history of malignant neoplasm within the previous five years and a history of chronic inflammatory diseases, such as arthritis, lupus or inflammatory bowel disease.

The study participants were categorized as low- (<10%, 0-1 risk), moderate- (<10%, >2 risk), high- (10-20%) or very high (>20%)-risk according to the number of coronary risk factors from the Framingham risk score assessment (modified by the National Cholesterol Education Program Adult Treatment Panel [NCEP ATP] III[11, 12]. In this risk scoring system, the level of coronary risk is considered to increase in association with increasing age, total cholesterol and systolic blood pressure, decreasing HDL-C, smoking and a male gender.

Data Collection Methods

Information regarding a patient's cardiovascular risk factors (age, sex, hypertension, smoking, diabetes mellitus, personal and family history of CHD and laboratory findings (lipid profile, the hsCRP level, the glycosylated hemoglobin [HbA1c] level) was collected from the patient's hospital records. The body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Hypertension was defined as a systolic blood pressure of >140 mmHg or a diastolic blood pressure of >90 mmHg measured after five minutes of rest on at least two occasions or the use of antihypertensive agents. Diabetes mellitus was defined as a fasting blood sugar level of >126 mg/dL or a postprandial 2-hour level of >200 mg/dL or the use of oral hypoglycemic agents

Table 1. Baseline clinical and laboratory characteristics

	Total ($n=1561$)	Men ($n=841$)	Women ($n=720$)	p-value
Age (years)	59.6 ± 12.4	57.5 ± 12.7	62.0 ± 11.7	<0.001
Weight (kg)	65.0 ± 11.2	69.9 ± 10.1	59.2 ± 9.5	<0.001
Height (cm)	161.8 ± 9.1	168.0 ± 6.1	154.6 ± 6.3	<0.001
BMI (kg/m^2)	24.7 ± 3.2	24.7 ± 2.9	24.7 ± 3.6	0.833
Waist circumference (cm)	88.0 ± 9.0	89.2 ± 8.0	86.4 ± 9.9	0.001
SBP (mmHg)	125.5 ± 16.7	125.6 ± 16.0	125.3 ± 17.5	0.737
DBP (mmHg)	75.3 ± 11.5	75.9 ± 11.5	74.6 ± 11.5	0.022
Smoking	274 (17.6)	252 (30.0)	22 (3.1)	<0.001
Hypertension	1054 (67.5)	569 (67.7)	485 (67.4)	0.901
Diabetes mellitus	308 (19.7)	174 (20.7)	134 (18.6)	0.304
Coronary heart disease	703 (45.0)	420 (49.9)	283 (39.3)	<0.001
F/Hx of CHD	42 (2.7)	24 (2.9)	18 (2.5)	0.667
Use anti-HBP medication	940 (60.2%)	503 (59.8%)	437 (60.7%)	0.722
TC (mg/dL)	189.6 ± 43.6	182.7 ± 41.6	197.7 ± 44.5	<0.001
LDL-C (mg/dL)	117.3 ± 38.9	112.4 ± 37.7	123.1 ± 39.6	<0.001
HDL-C (mg/dL)	47.8 ± 13.5	44.7 ± 12.6	51.4 ± 13.6	<0.001
TG (mg/dL)	146.3 ± 112.8	151.4 ± 131.2	140.4 ± 86.4	0.052
HbA1c (%)	6.48 ± 1.32	6.43 ± 1.25	6.55 ± 1.40	0.271
hsCRP (mg/L)	0.29 (0.01-7.48)	0.35 (0.01-7.48)	0.23 (0.01-7.45)	<0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; F/Hx, family history; CHD, coronary heart disease; HBP, hypertension; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; HbA1c, glycosylated hemoglobin; hsCRP, high-sensitivity C-reactive protein.

or insulin.

The serum hsCRP levels were measured using a high-sensitivity immunoturbidimetric method.

Statistical Analysis

Continuous variables are described as the mean ± standard deviation (SD) and were compared using unpaired *t*-tests. Due to the skewed distribution of the hsCRP levels, the comparisons were made using the Mann-Whitney *U* test or natural log transformation. Categorical variables are described as counts and percentages and were compared using either the chi-square test or Fisher's exact test (both nonparametric). The correlation coefficients between the hsCRP levels and continuous variables were calculated using Pearson's correlation coefficients and a Pearson's univariate correlation analysis, and a stepwise multiple linear regression analysis was used to determine whether the cardiovascular risk factors were associated with the hsCRP level. All tests were two-tailed. *p*-values of <0.05 were considered to indicate statistical significance. All of the statistical analyses were performed using the SPSS 15.0 software program (Statistical Package for the Social Sciences, SPSS-PC Inc, Chicago, Ill).

Results

Baseline Clinical and Laboratory Characteristics

The general characteristics and laboratory findings of the 1,561 subjects (841 men and 720 women) are listed in **Table 1**. The mean age was 59.6 years; the men were younger than the women (57.5 versus 62.0 years, respectively). The mean (± SD) and median (range) values of the hsCRP level were 1.32 (9.69) and 0.29 (0.01-7.48) mg/L, respectively. As expected, there were differences between the men and women in physical findings, the smoking status, CHD and lipid profiles: the men had a higher incidence of CHD, higher hsCRP levels, lower total cholesterol (TC) levels, lower LDL-C levels and lower HDL-C levels than the women (**Table 1**). The men had higher weights and heights; however, BMI did not differ significantly between the men and women. The prevalence of hypertension and diabetes mellitus was not significantly different between the men and women (**Table 1**).

Relationship Between the hsCRP Level and Cardiovascular Risk Factors

The prevalence of the cardiovascular risk factors and coronary heart disease and the associated median hsCRP levels are listed in **Table 2**. With the exception

Table 2. Level of hsCRP according to the presence of individual coronary heart disease risk factors and coronary heart disease

	Yes		No		p-value[†]
	n (%)	Median hsCRP (mg/L)	n (%)	Median hsCRP (md/L)	
Smoking	274 (17.6)	0.28	1287 (82.4)	0.27	0.248
Hypertension	1054 (67.5)	0.32	507 (32.5)	0.18	<0.001
HDL-C <40 mg/dL	427 (27.4)	0.36	1134 (72.6)	0.17	<0.001
F/Hx of premature CHD	42 (2.7)	0.34	1519 (97.3)	0.22	0.001
Age (M ≥45; F ≥55)	1255 (80.4)	0.31	306 (19.6)	0.17	<0.001
LDL-C >100 mg/dL	1005 (64.4)	0.22	556 (35.6)	0.38	<0.001
CHD	703 (45.0)	0.45	858 (55.0)	0.19	<0.001

hsCRP, high-sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; F/Hx, family history; CHD, coronary heart disease; M, male; F, female.
[†]Mann-Whitney U test of the median hsCRP level between the yes group and the no group.

of smoking, the presence of each individual cardiovascular risk factor was associated with a higher median hsCRP level than that observed when the risk factor was absent (**Table 2**). The unadjusted correlation coefficients between log hsCRP and the number of cardiovascular risk factors showed that an increase in the number of cardiovascular risk factors was correlated with a significantly increased hsCRP level in the total patient population ($r=0.126$; $p<0.001$) and in men alone ($r=0.112$; $p=0.004$). **Table 3** shows the calculated quartiles of the hsCRP levels and the odds ratios (95% confidence intervals) for the incidence of cardiovascular disease between the hsCRP quartiles, adjusted for the various cardiovascular risk factors.

The hsCRP level was found to be significantly increased in each group from the low to very high risk groups in the total patient population and in men alone. The hsCRP levels classified according to the cardiovascular risk classification of the NCEP ATP Ⅲ guidelines were, from low to very high risk, 0.15, 0.23, 0.27 and 0.47, respectively, in the total patient population, 0.22, 0.22, 0.47 and 0.50, respectively, in men and 0.12, 0.32, 0.19 and 0.44, respectively, in women.

The quartiles of the hsCRP levels and the associations between the hsCRP quartiles and the cardiovascular risk factors are shown in **Table 4**. A univariate analysis showed that age, the HbA1c level, BMI, the HDL-C level, the LDL-C/HDL-C ratio, the LDL-C/TC ratio, the HDL-C/TC ratio, the HDL-C/TG ratio and the TC/TG ratio were significantly correlated with the hsCRP level (**Table 4**). In the multivariate analysis, we included variables with p-values of <0.1 in a univariate model, but excluded several ratios containing the HDL-C component. In the multivariate model, we included age, the HDL-C level, the HbA1c level, the LDL-C/TC ratio, the TC/triglyceride (TG)

Table 3. Independent predictors for coronary heart disease according to a multivariate regression analysis

	Odds ratio	95% CI	p-value
Age	1.037	1.021-1.053	<0.001*
Body mass index	0.998	0.952-1.045	0.920
Smoking	1.739	0.652-4.637	0.269
Total cholesterol	0.991	0.976-1.006	0.242
Triglycerides	1.003	1.000-1,006	0.042*
LDL-C	1.005	0.989-1.021	0.531
HDL-C	1.015	0.997-1.033	0.111
hsCRP 1 (Low)	1		
hsCRP 2	1.217	0.766-1.933	0.406
hsCRP 3	1.904	1.196-3.032	0.007*
hsCRP 4 (High)	1.907	1.155-3.150	0.012*

CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein.
*$p<0.05$; hsCRP 1, 0.01-0.08 mg/L; hsCRP 2, 0.09-0.29 mg/L; hsCRP 3, 0.30-0.92 mg/L; hsCRP 4, 0.93-7.48 mg/L

ratio and BMI. As shown in **Table 4**, age, the HDL-C level, the LDL-C/TC ratio and BMI were found to be significantly correlated with the hsCRP level.

Discussion

The present study demonstrated that the hsCRP levels are significantly higher in Korean patients with cardiovascular risk factors than in those without. In addition, in this study, the hsCRP levels were found to be significantly proportionate to increases in the number of cardiovascular risk factors and the degree of cardiovascular risk classification. This study provides evidence that age, the HDL-C level, the LDL-C/

Table 4. Univariate correlations and stepwise multiple regression analysis of the correlations between various parameters and the log transformed level of hsCRP in all study subjects

	Quartile of hsCRP (mg/L)				Univariate[†]		Multivariate[§]	
	0.01-0.08	0.09-0.29	0.30-0.92	0.93-7.48	r	p	β	p
n	394	397	378	392				
Age (years)	55.4 ± 13.6	59.7 ± 11.4	61.2 ± 11.5	62.2 ± 12.0	0.152	<0.001	0.015	<0.001
TC (mg/dL)	192.2 ± 39.2	194.5 ± 42.5	188.6 ± 46.4	182.4 ± 44.4	−0.039	0.124	−	−
LDL-C (mg/dL)	117.9 ± 34.0	122.3 ± 43.0	114.3 ± 38.1	113.0 ± 38.8	0.009	0.737	−	−
HDL-C (mg/dL)	50.5 ± 13.6	48.8 ± 13.7	46.0 ± 11.8	43.8 ± 13.2	−0.181	<0.001	−0.016	<0.001
LDL-C/HDL-C ratio	2.33 ± 1.16	2.51 ± 1.01	2.48 ± 0.93	2.58 ± 0.92	0.143	<0.001	−	−
LDL-C/TC ratio	0.61 ± 0.11	0.63 ± 0.09	0.61 ± 0.08	0.62 ± 0.12	0.085	0.001	0.766	0.038
HDL-C/TC ratio	0.26 ± 0.08	0.25 ± 0.08	0.24 ± 0.07	0.24 ± 0.08	−0.138	<0.001	−	−
HbA1c (%)	6.01 ± 1.10	6.46 ± 1.17	6.72 ± 1.48	6.51 ± 1.23	0.167	<0.001	−	−
BMI (kg/m²)	23.8 ± 4.0	24.4 ± 3.6	25.1 ± 3.9	25.3 ± 3.6	0.072	0.005	0.046	<0.001
TG (mg/dL)	141.1 ± 77.3	154.5 ± 104.2	144.0 ± 86.8	147.1 ± 101.3	0.004	0.887	−	−
HDL-C/TG ratio	0.36 ± 0.32	0.34 ± 0.35	0.30 ± 0.29	0.29 ± 0.33	−0.107	<0.001	−	−
LDL-C/TG ratio	0.84 ± 0.69	0.85 ± 0.61	0.74 ± 0.58	0.77 ± 0.63	−0.023	0.388	−	−
TC/TG ratio	1.36 ± 0.96	1.35 ± 0.90	1.22 ± 0.85	1.23 ± 0.93	−0.061	0.018	−	−

hsCRP, high-sensitivity C-reactive protein; r, Pearson's correlation coefficients; β, standardized regression coefficients; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; HbA1C, glycosylated hemoglobin; BMI, body mass index; TG, triglycerides.
[†]Pearson's univariate correlation analysis; [§]stepwise multivariate regression analysis.

TC ratio and BMI are independent factors correlated with the hsCRP level.

The inflammatory response is now considered to play a key role in the development and progression of atherosclerosis[13]. Acute reactant hsCRP, an important marker of inflammation, appears to stimulate endothelial dysfunction and promote inflammation in the vessel wall, thus contributing to the initiation and progression of atherogenesis[13, 14] and an increased risk of cardiovascular events[15, 16].

Several prospective epidemiologic and randomized controlled studies of statin therapy have shown that the hsCRP level is either an independent predictor of future cardiovascular risk[7, 17-19] or provides additive value, together with other traditional risk factors, for predicting cardiovascular events[20, 21]. However, the present study is the first large, observational, multicenter study to show that the hsCRP level is significantly associated with cardiovascular risk factors in Korean subjects with cardiovascular disease or diabetes mellitus.

According to the NCEP ATP Ⅲ study, cardiovascular risk factors that modify LDL-C goals include smoking, hypertension, a low HDL-C level, a family history of premature CHD and an old age. Our study showed that the hsCRP level is correlated with each individual cardiovascular risk factor, except for smoking. It is conceivable that components of cardiovascular risk factors promote or are correlated with atherosclerosis, which involves inflammatory processes. Our study showed that the hsCRP level is significantly correlated with conventional coronary risk factors, such as age and BMI, which were adjusted for in the total cohort.

Interestingly, among lipid profiles, only the HDL-C level was found to be significantly associated with the hsCRP level (**Table 4**). The mechanisms underlying the adverse effects of an elevated CRP level on lipid metabolism remain unclear; however, the results observed in the present study suggest that the hsCRP level may be an inverse predictor of the HDL-C level in Korean subjects with cardiovascular disease or diabetes mellitus.

Previous studies have indicated that the TC/HDL-C ratio is a significant predictor of cardiovascular events and a therapeutic target in high-risk patients, with reductions in this parameter being achieved with the use of more aggressive LDL-C-lowering therapy or by potentially increasing the HDL-C level[22-26]. Many studies examining the associations between the hsCRP level and lipid profiles differ in their results due to differences in age composition, sample size and various other factors. Although no correlations between the hsCRP and LDL-C levels were observed in the present study, these two parameters were found to be minimally correlated in a previous study conducted in healthy American women[8], and the combined evaluation of the CRP and LDL-C levels has been found to

be superior for risk detection compared to measuring either parameter alone. Overall, this study showed that the CRP level is actually a stronger predictor of future cardiovascular events than the LDL-C level and adds prognostic value to the Framingham risk assessment[8]. Many studies have demonstrated the additive value of the hsCRP level in predicting cardiovascular risk; however, other studies have reported that measuring the level of CRP adds no additional value for coronary risk prediction when traditional cardiovascular risk factors are assessed[27, 28]. Paul Elliott and colleagues reported little concordance between CRP genotypes and the CRP level and its effects on CHD[29].

It has not yet been established whether inflammatory markers, such as the hsCRP level, are useful for predicting cardiovascular risks, and measuring inflammatory markers to evaluate future cardiovascular events is not routinely recommended.

Our study is associated with some limitations. Firstly, we used a cross-sectional and observational design that did not allow us to evaluate the temporal relationship between future cardiovascular events and the hsCRP level. Our findings should be confirmed in future adequately powered, prospective trials. Second, the study participants were patients with diabetes mellitus or cardiovascular diseases, such as hypertension or coronary heart disease (CHD); therefore, our population was very heterogeneous and is not representative of the general population of Korea. Third, patients receiving statin or lipid-lowering treatment within three months prior to measuring their hsCRP level were excluded from this study. Therefore, it is possible that a number of patients with high LDL-C levels were excluded, while patients with low HDL-C levels were included. Finally, data regarding various factors that are associated with raised hsCRP levels, such as a high protein diet, sedentary lifestyle, sleep deprivation and alcohol use, were not available to the investigators.

Regardless of these limitations, the results of this study suggest that there is a significantly proportionate relationship between the hsCRP level and the degree of cardiovascular risk assessed according to the NCEP ATP Ⅲ classification. It is likely that no one solitary pathway is responsible for all cardiovascular events and that interactions between various risk factors are important. As atherothrombosis often occurs in the absence of hyperlipidemia, identifying biomarkers that can be used as alternatives or adjuncts to the LDL-C level is warranted. The CRP level remains reasonably stable over long periods of time and is relatively inexpensive to measure[8]. The results of the present study suggest that the hsCRP level may offer considerable additive value in predicting cardiovascular risks in Korean populations. Reducing the hsCRP level by means of anti-inflammatory medications, such as statins, may therefore decrease future cardiovascular risks.

Conclusions

In Korean subjects with cardiovascular disease or diabetes mellitus, the hsCRP level exhibits a significantly proportionate relationship to the degree of cardiovascular risk and may provide additive value in predicting cardiovascular risks. Assuming that the hsCRP level reflects future cardiovascular risks, interventions that reduce the hsCRP level may be effective in reducing the incidence of cardiovascular events.

Acknowledgments

Conflicts of Interest

None.

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