ORIGINAL ARTICLE

High-Sensitivity C-Reactive Protein and Ankle Brachial Index in a Finnish Cardiovascular Risk Population

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ABSTRACT

High-sensitivity C-reactive protein (hsCRP) has been previously linked to different forms of vascular disease. However, some studies have not found any relationship between hsCRP and atherosclerosis. Also, studies investigating correlation between hsCRP and ankle brachial index (ABI) are scarce. We studied hsCRP in a cardiovascular risk population with a special interest in correlation between hsCRP and ABI. All men and women aged 45 to 70 years from a rural town Harjavalta, Finland were invited to participate in a population survey. Diabetics and people with known vascular disease were excluded. Seventy-three percent ($n = 2085$) of the invited persons participated and 70% of the respondents ($n = 1496$) had at least one risk factor to cardiovascular diseases. These subjects were invited to further examinations. From them we measured ABI, hsCRP, leukocyte count, glucose tolerance, systemic coronary risk evaluation (SCORE), body mass index (BMI), and waist circumference. Mean hsCRP was 1.9 mg/L. Smokers had higher hsCRP (mean 2.2 mg/L) than nonsmokers (mean 1.8 mL/L). hsCRP in women was higher than in men (mean 2.0 mg/L versus 1.8 mg/L). Mean ABI was 1.10, and the prevalence of peripheral arterial disease was 3.1%. ABI correlated weakly with hsCRP ($r = -0.077$, $p = 0.014$), leukocyte count ($r = -0.107$, $p = 0.001$), and SCORE ($r = -0.116$, $p = 0.001$). It did not have correlation between age, weight, BMI, or waist circumference. hsCRP correlated with BMI ($r = 0.208$, $p < 0.0001$) and waist circumference ($r = 0.325$, $p < 0.0001$). When we excluded subjects with hsCRP >10 mg/L, ABI no longer correlated with hsCRP. In a cardiovascular risk population, hsCRP has only a weak correlation with ABI, and this correlation disappeared when we excluded subject with hsCRP >10 mg/L. Instead, hsCRP was correlated to the measures of obesity (waist circumference and BMI), indicating its role as a marker of adipose tissue–driven inflammation. hsCRP does not seem to be a suitable screening method for peripheral arterial disease.

KEYWORDS: High sensitivity C-reactive protein, ankle brachial index, cardiovascular risk factors

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C-reactive protein (CRP) is an acute phase protein. In everyday practice, it has been used in the diagnosis and monitoring of acute inflammation and infection. High-sensitivity CRP (hsCRP) techniques are able to measure concentrations of hsCRP as small as 0.15 mg/L. Some recent studies have shown that hsCRP is a predictor for peripheral arterial disease (PAD), myocardial infarction, and stroke.[1–3] According to hsCRP, three risk groups have been identified: a low-risk group (hsCRP <1 mg/L), a moderate-risk group (hsCRP 1 to 3 mg/L), and a high-risk group (hsCRP >3 mg/L).[4] However, some studies did not find any relation between hsCRP and atherosclerosis.[5,6] Saito et al also concluded that hsCRP is involved in the interrelation of other cardiovascular risk factors (age, smoking, obesity, high blood pressure, and dyslipidemia) and that these traditional risk factors provoke cardiovascular disease.[7] In addition, studies on the relation between hsCRP and levels of ankle brachial index (ABI) are scarce. One of them shows a weak independent, inverse relation between hsCRP and ABI only in men.[8] Elias-Smale et al discovered that hsCRP levels gradually rose with decreasing ABI in both genders, especially in subjects with ABI <0.91.[9] High hsCRP levels seemed to be associated with PAD also in patients without cardiovascular disease, diabetes (DM), or hypertension in the study of Shankar et al.[10] Vu et al studied the impact of hsCRP on the likelihood of PAD in patients with the metabolic syndrome (MS), DM, or preexisting cardiovascular disease.[11] The likelihood of PAD was enhanced by elevated hsCRP levels in adults with MS and DM, but not in those with preexisting cardiovascular disease. Therefore, there is still some controversy in these findings, and the relationship between ABI and hsCRP is unclear. In our study, we correlated ABI to known risk factors of atherosclerosis and PAD. We had a special interest in correlation between hsCRP and ABI.

METHODS

We invited all men and women aged 45 to 70 years from a rural town Harjavalta, Finland (population 7700 inhabitants) to participate in a population survey. Diabetics and people with known cardiovascular disease were excluded. The aim was to detect a cardiovascular risk population. An invitation to the project was mailed to 2856 persons, and it included a risk factor survey, tape measure, and Finnish Diabetes Risk Score (FINDRISC) questionnaire.[12] In the risk factor survey, the subjects were asked about their waist circumference measured at the level of navel, latest measured blood pressure, possible antihypertensive medication, gestational diabetes, hypertension, and family burden to cardiovascular diseases (parents or siblings having coronary heart disease, myocardial infarction, or stroke) and smoking habits. If subjects were willing to participate in the study, they mailed the risk factor survey back to the health center. Seventy-three percent ($n = 2085$) of the invited persons participated. Seventy percent of the respondents ($n = 1496$) had at least one risk factor to cardiovascular diseases. Waist circumference $\geq$80 cm for women and $\geq$94 cm for men, systolic blood pressure (SBP) $\geq$140 mm Hg or diastolic blood pressure (DBP) $\geq$90 mm Hg, or at least 12 points in the FINDRISC were considered as risk factors along with any positive answer to questions in risk factor survey.

These subjects were invited to further examinations, and if they were diagnosed with hypertension, DM, impaired glucose tolerance (IGT), impaired feasting glucose (IFG), or MS or had a body mass index (BMI) $\geq$30 kg/m^2 or a 10-year risk of cardiovascular death of 5% or more based on the SCORE (Systematic Coronary Risk Evaluation) system,[13] they were physically examined by a doctor, and the ABI measurement was taken. Hypertension was defined as the use of antihypertensive medication or as the mean of home blood pressure monitoring $\geq$135 mm Hg for SBP or $\geq$85 mm Hg for DBP.[14] If study subjects had no antihypertensive medication at enrollment and the study nurse measured SBP $\geq$140 mm Hg or DBP $\geq$90 mm Hg, subjects were taught to use an automatic validated blood pressure monitor (Omron® M4–1; Omron, Tokyo, Japan), which was lent to them for home blood pressure monitoring. The subjects whose arm circumference was >32 cm used a larger cuff. The subjects were instructed to take duplicate blood pressure measurements in the seated position after 5 minutes of rest in the morning and evening for 1 week.

The recorded measurements except those from the first day were used to calculate the mean home blood pressure, as recommended by the recent guidelines of the European Society of Hypertension.[14] All the ABI measurements were made by two measurers, a doctor or a trained nurse. ABI was determined from blood pressure measurements in the arms and ankles with the patient in supine position. SBP in the brachial artery was measured in both upper arms using a blood pressure cuff and Doppler instrument (UltraTec® PD1v with a vascular probe of 5 MHz; Medema T/A Omega Medical Supplies Ltd., London, United Kingdom) in the antecubital fossa. SBP was measured from both lower limbs, placing the cuff just above the level of malleoli. ABI was the lower ankle SBP divided by the higher brachial SBP.

The laboratory tests were determined in blood samples obtained after at least 12 hours of fasting. An oral glucose tolerance test was performed by measuring fasting plasma glucose and a 2-hour plasma glucose from capillary whole blood after ingestion of a glucose load of 75 g with the HemoCue® Glucose 201 + system (HemoCue AB, Ängelholm, Sweden), which converts the result from capillary whole blood to plasma glucose values. Glucose disorders were classified according to

Table 1 Correlation of ABI and hsCRP to Each Other and to Waist Circumference, Leukocyte Count, and SCORE

	ABI	hsCRP	Waist Circumference	Leukocyte Count	SCORE
ABI		$r=-0.077$	$r=0.032$	$r=-0.107$	$r=-0.116$
		$p=0.014$	$p=0.312$	$p=0.001$	$p=0.001$
hsCRP	$r=-0.077$		$r=0.325$	$r=0.215$	$r=0.060$
	$p=0.014$		$p<0.001$	$p<0.0001$	$p=0.077$

Pearson correlation (r) analysis. ABI, ankle brachial index; hsCRP, high sensitivity C-reactive protein; SCORE, systemic coronary risk evaluation.

the World Health Organization 1999 criteria, updated in 2006.[15] On the basis of 2-hour postload plasma glucose, individuals were classified into categories of newly diagnosed diabetes, IGT, and normal glucose tolerance if their 2-hour plasma glucose concentrations were ≥12.2, 8.9 to 12.1, and <8.9 mmol/L, respectively. Impaired fasting glucose was diagnosed if the fasting plasma glucose was ≥6.1 mmol/L and the 2-hour plasma glucose was <8.9 mmol/L. hsCRP was analyzed by Konelab 60i analyzer (Thermo Electron, Vantaa, Finland). A second analysis was made including only subjects with hsCRP under 10 mg/L ($n=991$) because of the possibility of acute infection in subjects with hsCRP values over 10 mg/L. Subjects aged 64 years or older were considered to have elevated risk of cardiovascular disease because of their age, and SCORE was not determined for them.

MS was diagnosed according to the criteria of International Diabetes Federation (IDF)[16] and the U.S. National Cholesterol Education Program (NCEP) Third Adult Treatment Panel.[17] All of the participants provided written informed consent for the project and subsequent medical research. The study protocol and consent forms were reviewed and approved by the ethics committee of Satakunta Hospital District. A detailed description of the enrollment and examination methods has been published earlier.[18]

Statistical Analysis

Statistical analyses were performed using the SAS System for Windows, version 9.1. We used different tests: t test, one-way analysis, Pearson correlation test, and stepwise multivariable analysis. A natural logarithm transformation was made for hsCRP data. The data are expressed as mean and standard deviation (SD) in parenthesis, and p value <0.05 is considered as statistically significant.

RESULTS

The mean age of the subjects was 58.6 years. From the study population, 182 (17%) were smokers and 865 (83%) were nonsmokers. MS was diagnosed in 599 (57%) of the subjects according to IDF criteria and in 480 (46%) according to NCEP criteria. Seventy-four subjects (7%) had DM, 391 (37%) had IFG, and 179 (17%) IGT.

Mean hsCRP (SD) was 1.9 mg/L (3.0 mg/L). There was a statistically significant difference between hsCRP in smokers [mean 2.2 mg/L (2.9 mg/L)] and nonsmokers [mean 1.8 mg/L (3.5 mg/L); $p=0.050$]. Women had higher hsCRP values than men; mean hsCRP in women was 2.0 mg/L (3.1 mg/L) and in men was 1.8 mg/L (2.9 mg/L, $p=0.058$). Mean ABI was 1.10 (range 0.56 to 1.64). Number of subjects with ABI ≤0.90 indicating PAD was 32 (3.1%). Only three subjects had ABI ≥1.5. In Pearson correlation analysis, ABI had a weak, although statistically significant, negative correlation to hsCRP ($r=-0.077$; $p=0.014$), leukocyte count ($r=-0.107$; $p=0.001$), and SCORE ($r=-0.116$; $p=0.001$). No statistically significant correlation was found between ABI and age, ABI and weight, ABI and BMI, or ABI and waist circumference. A moderate positive correlation was found between hsCRP and BMI ($r=0.208$, $p<0.0001$). HsCRP also had correlation between waist circumference ($r=0.325$, $p<0.0001$; Table 1).

In multivariate analysis (explanatory factors: BMI class, glucose disorders, ABI, waist circumference, high-density lipoprotein, triglycerides, leukocyte count), the correlation between hsCRP and BMI was confirmed ($p<0.0001$) as well as the correlation between hsCRP and waist circumference ($p=0.047$). No statistically significant correlation was found between hsCRP and ABI ($p=0.071$).

When the data were analyzed leaving out the subjects with hsCRP >10 mg/L, women had higher hsCRP values than men; mean hsCRP was 1.8 mg/L (2.8 mg/L) in women and 1.5 mg/L (2.5 mg/L) in men ($p=0.013$). There was no statistically significant difference between hsCRP values in smokers and nonsmokers ($p=0.44$). In Pearson correlation analysis, ABI correlated weakly with leukocyte count ($r=-0.090$, $p=0.006$) and SCORE ($r=-0.106$, $p=0.003$) but did not correlate with hsCRP. A positive correlation ($r=0.295$) was found between hsCRP and waist circumference ($p<0.0001$).

DISCUSSION

HsCRP has previously been linked with PAD. In the study of Pande et al, a 2.2-fold increase in the prevalence of PAD was found in subjects with a high CRP (>3 mg/L) compared with subjects with low CRP (<1 mg/L).[19]

This relationship persisted only in subjects without insulin resistance. Because atherogenesis is a sum of multiple risk factors, it might be that in individuals with few risk factors, inflammation has a large contribution to the development of vascular disease, whereas in the presence of a strong risk factor like insulin resistance, this contribution is diminished. Eldrup et al have also shown that ABI <0.9 is superior to CRP in identifying individuals with severe atherosclerosis.[20]

Our study indicates that there is only a weak correlation between ABI and hsCRP; subjects with lower ABI had higher hsCRP values, and this relation disappeared in multivariate analysis and when leaving out subjects with hsCRP >10 mg/L. One reason for this may be that we studied a cardiovascular risk population. In addition, the prevalence of MS, obesity, and glucose disorders were high in our study population. As discussed later, all of these risk factors are strongly associated with inflammatory process. This is in line with the recently published study by Bo et al in which there was no independent association between hsCRP and peripheral subclinical atherosclerosis in subjects with moderate to high risk of cardiovascular disease.[21] In the study of Shankar et al,[10] hsCRP was associated with PAD independently of major cardiovascular risk factors (smoking, waist circumference, BMI, blood pressure, glycosylated hemoglobin, serum total cholesterol, and other confounders). However, they studied subjects without cardiovascular disease, diabetes, or hypertension. In our study group, the mean hsCRP was 1.9 mg/L, indicating a moderate-risk population.[4]

We found a correlation between hsCRP and BMI and waist circumference. This finding is in line with the study of Hak et al, who found that hsCRP was related to BMI and to waist and hip circumferences separately; however, after adjustment for BMI, waist circumference was still related to hsCRP, whereas hip circumference was not. Thus it seems that abdominal fat deposition may be the most important factor contributing to inflammation.[22] The same kind of finding was made by Ford about the correlation between hsCRP and BMI.[23]

Previously it has been shown that PAD is not associated with BMI but waist-hip ratio is.[24] BMI is not the best possible measure of intra-abdominal adiposity, which drives the progression of cardiovascular risk factors through secretion of adipokines and exacerbation of insulin resistance.[25]

One study indicated smaller BMI values in patients with ABI under 0.9.[26] This shows that adipose tissue mediated inflammation is only one factor leading to PAD. In our study, there was no statistically significant correlation between BMI and ABI. In this study, hsCRP was higher in smokers than in nonsmokers (however only before excluding subjects with hsCRP >10 mg/L) and in women compared with men with a borderline significant p value. Increased levels of inflammatory markers have been measured previously among smokers.[27]

HsCRP has been associated more strongly with female than male obesity.[28] A recent study showed that hsCRP was higher in smoking men compared with nonsmoking men. This difference was not detected between smoking and nonsmoking women in a nondiabetic population, indicating that smoking might associate differently with subclinical inflammation between genders.[29] In our study population, the majority of participants were women.

We did not find a statistically significant correlation between age and ABI, but the trend was that older patients had lower ABI ($r = 0.04$, $p = 0.198$), and only three patients with ABI <0.9 were under 60 years old. This may be caused by the fact that the oldest subjects were 70 years of age and the prevalence of PAD almost doubles after the age of 70.[26]

The lower ankle pressure was used for ABI calculation. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) guidelines[30] recommend measuring both posterior tibial artery and dorsal pedal artery pressures and using the higher of the ankle pressures to calculate ABI, which may better address leg perfusion. However, the method we used has been shown to identify a higher number of patients with increased risk for future cardiovascular events.[31] TASC II[30] recommends that ABI should be screened to detect PAD from the patients with exertional leg symptoms, patients between 50 and 69 years old with a cardiovascular risk factor (particularly diabetes or smoking), patients over 70 years old despite the risk status, and patients with Framingham risk score from 10 to 20%.

CONCLUSIONS

Our study indicates that in this Finnish subpopulation of subjects with cardiovascular risk factors, hsCRP is not a suitable screening method for PAD. Instead, hsCRP correlated to measures of obesity (waist circumference and BMI), indicating its role as a marker of adipose tissue driven inflammation.

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