Original Article

Single-Photon Emission Computed Tomography Myocardial Ischemia Detection in High-Risk Asymptomatic Patients: Correlation with Coronary Calcium Score and High-Sensitivity C-Reactive Protein

Irena Mitevska, Elizabeta Srbinovska, Lily Stojanovska[1], Emilija Antova[1], Vasso Apostolopoulos[1], Marijan Bosevski

Department of Nuclear Cardiology, University Cardiology Clinic, Skopje, Macedonia, [1]Department of Nuclear Cardiology, Victoria University, Melbourne, Australia

Abstract

Background: The association between myocardial ischemia in high-risk patients with coronary calcium score (CCS) and high-sensitivity C-reactive protein (hs-CRP) is not well established. **Aims:** We evaluated the correlation between hs-CRP, CCS, and myocardial ischemia in asymptomatic high-risk patients without known coronary artery disease (CAD). **Materials and Methods:** We prospectively assessed 68 asymptomatic high-risk outpatients without known CAD. One-day rest-stress Tc-99m single-photon emission computed tomography (SPECT) myocardial perfusion imaging and multislice computed tomography were performed. Multivariate regression analysis was performed for the assessment of predictors of myocardial ischemia. Standard risk factors and hs-CRP values were analyzed. **Results:** CCS >0 Agatston score was observed in 26 patients (46.4%). Seven patients had CCS between 10 and 99 AU, 8 patients between 100 and 400 AU, and 11 patients had CCS >400 AU. Mild ischemia was noted in 11 patients, moderate ischemia in 10 patients, and severe ischemia in 6 patients. Hs-CRP was >1 mg/L in 39 patients, of whom 8 patients had CCS >0, 13 patients had normal SPECT results, 6 patients had mild ischemia, and 12 patients had moderate and severe ischemia. Multivariate regression analysis showed independent predictors for increased CCS: low-density lipoprotein cholesterol (odds ratio [OR]: 2.891; $P = 0.001$); age >70 years (OR: 2.568; $P = 0.001$); and smoking (OR: 1.931; $P = 0.001$). We found hs-CRP to be an independent predictor of myocardial ischemia (OR: 4.145; 95% confidence interval: 1.398–7.471, $P = 0.001$). **Conclusion:** hs-CRP was an independent predictor of myocardial ischemia. hs-CRP might improve the selection of high-risk asymptomatic patients for myocardial SPECT imaging.

Keywords: *Coronary Artery Calcium Score, high-sensitivity C-reactive protein, single-photon emission computed tomography myocardial imaging*

Introduction

The vast amount of evidence suggests that inflammation has a major role in the development of atherosclerosis and its clinical manifestations.[1,2] High-sensitivity C-reactive protein (hs-CRP) is the most studied and clinically evaluated inflammatory marker. The latest European guidelines on cardiovascular (CV) prevention recommend this marker for additional risk stratification in selected patients.[3] Practical use of inflammatory markers is distinctive and can help refine the patient's risk and our clinical reasoning. In some studies, plasma values of hs-CRP predicted increased cardiac events (myocardial infarction and cardiac death). hs-CRP is increased in diabetic patients and is associated with numerous traditional risk factors, including hypertension, dyslipidemia, smoking, and obesity.[4,5] There are conflicting positions concerning the correlation between hs-CRP and stable coronary artery disease (CAD) based on some clinical studies.[6] The association between hs-CRP and clinical events is related to the extensity and complexity of atherosclerosis and the risk factors leading to unstable disease. The debate persists concerning the association between hs-CRP and atherosclerotic burden, myocardial ischemia, and coronary events.[7-9] Some scientific data argue that hs-CRP might define the phenotypic vascular expression of atherosclerosis in patients with similar risk factors. The commercial availability of hs-CRP assays has made screening for this marker simple and highly reproducible.

How to cite this article: Mitevska I, Srbinovska E, Stojanovska L, Antova E, Apostolopoulos V, Bosevski M. Single-photon emission computed tomography myocardial ischemia detection in high-risk asymptomatic patients: Correlation with coronary calcium score and high-sensitivity C-reactive protein. Indian J Nucl Med 2019;34:99-106.

Address for correspondence:
Dr. Irena Mitevska, University Cardiology Clinic, Ul. Vodnjanska 17, 1000 Skopje, Macedonia.
E-mail: peovskai@yahoo.com

Access this article online

Website: www.ijnm.in

DOI: 10.4103/ijnm.IJNM_152_18

Quick Response Code:

Myocardial single-photon emission computed tomography (SPECT) imaging is a well-established method for the assessment of myocardial ischemia. Myocardial ischemia severity and extensity is a very well-established prognostic parameter with a large number of prognostic studies using SPECT imaging.[9] It is of clinical interest to define the association between hs-CRP levels, atherosclerosis, and ischemic myocardium. coronary calcium score (CCS) is a marker of atherosclerotic burden and a parameter that reclassifies patient risk. The amount of CCS is a predictor of CV events in symptomatic and asymptomatic patients.[10] Data correlating hs-CRP with the presence of myocardial ischemia are conflicting, in addition to the correlation between hs-CRP and CCS. Some studies note a correlation between hs-CRP and CCS, whereas others have shown no significant association.[10,11] It is unknown whether these conflicting data reflect the limitations of each study design or real differences in the pathophysiological mechanisms of CAD. The problem is even more complex, keeping in mind that there is no confirmed linear correlation between CCS and the presence and extensity of SPECT myocardial ischemia and how inflammatory activity might influence those two different CAD expressions.[10] In this study, we aimed to determine further scientific insights into this clinically challenging topic.

Materials and Methods

Study design and protocol

This nonrandomized, prospective, clinical study evaluated 68 consecutive asymptomatic high-risk patients based on the European SCORE model (SCORE risk for events >10), without previously known or established CAD (41 males and 27 females with a mean age of 64 ± 7.2 years). Screening for myocardial ischemia was performed using myocardial perfusion imaging (MPI) SPECT imaging in the nuclear cardiology laboratory at our clinic. Coronary Artery Calcium Score was evaluated using multisliced computed tomography.

This study is part of a research thesis data, approved by the Ethics Committee of the Medical Faculty, University St. Cyril and Methodius in Skopje, Republic of Macedonia. Informed consent was signed by all the included patients. There was no financial support for the study.

Patients' risk assessment

The European SCORE model was used for risk assessment of the patients. High-risk criteria were the following: markedly elevated single risk factors, in particular cholesterol >8 mmol/L or blood pressure (BP) >180/110 mmHg, diabetics mellitus (DM) without major risk factors that may be at low or moderate risk, moderate chronic kidney disease (CKD) (GFR: 30–59 mL/min/1.73 m^2), and calculated SCORE >5% and <10%. Very high-risk criteria were patients with any of the following: stroke and transient ischemic attack, aortic aneurysm, and peripheral artery disease. Unequivocally documented CV disease (CVD) on imaging includes plaque on carotid ultrasound, DM with target organ damage (proteinuria or presence of major risk factors such as smoking, hypercholesterolemia, or marked hypertension), severe CKD (GFR <30 mL/min/1.73 m^2), and calculated SCORE >10%.

Physical examination of all the patients was performed which included BP measurement. Laboratory examination was performed in all patients 2 ± 1 week before the MPI study and included the following parameters: full blood count, fasting glucose level, description glycated hemoglobin (HbA1c)%, blood urea nitrogen, creatinine, electrolytes – sodium and potassium, aspartate aminotransferase, alanine aminotransferase, fasting lipid values – cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride, and non-HDL cholesterol.

Renal function was assessed using modification of diet in renal disease (MDRD) study equation formula for the assessment of glomerular filtration rate (GFR). The following staging of renal function was used: GFR >90 mL/min/1.73 m^2 – normal renal function, GFR 60–89 mL/min/1.73 m^2 – mild renal dysfunction, and GFR 30–59 mL/min/1.73 m^2 – moderate renal dysfunction.

hs-CRP was evaluated in all patients by immunoturbidimetric method using Abbott Architect® c8000 assay, with analytical sensitivity 0.1–5 mg/L. hs-CRP values of <1 mg/L were defined as low risk, 1–3 mg/L as moderate risk, and >3 mg/L as high risk for CV events.

Clinical and laboratory characteristics are shown in Table 1. The following inclusion criteria were used: asymptomatic patients with high CV risk; exclusion criteria were as follows: typical stable angina pectoris; previously known or

Table 1: Mean values of laboratory and clinical parameters

Variables	Mean values
Age	64.0±7.2
Systolic pressure (mmHg)	158.7±15.2
Diastolic pressure (mmHg)	90.2±7.6
Weight (kg)	84.1±9.2
Height (cm)	168.5±7.1
BMI (kg/m^2)	26.4±2.0
Total cholesterol (mmol/L)	4.8±1.1
HDL cholesterol (mmol/L)	0.9±0.4
Non-HDL cholesterol (mmol/L)	3.9±0.8
LDL cholesterol (mmol/L)	3.4±1.2
Hs-CRP	1.76±0.96
GFR (mL/min/1.73 m^2)	67.4±19.6

BMI: Body mass index, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, hs-CRP: High-sensitivity C-reactive protein, GFR: Glomerular filtration rate

established CAD (a history of myocardial infarction, acute coronary syndromes, previous percutaneous intervention, or coronary artery bypass surgery); left ventricular ejection fraction <50% at rest; severe valvular disease; atrial fibrillation; left bundle branch block; presence of pacemaker; severe chronic pulmonary and liver diseases; acute and chronic inflammatory process; active infections; systemic rheumatic and autoimmune diseases such as lupus, vasculitis, rheumatoid arthritis, and inflammatory bowel disease; and history of tumors and previous chemotherapy, hormone replacement therapy in women, and recent trauma. Patients with renal failure and GFR <30 mL/min/1.73 m^2 (MRDR formula) were excluded from the study due to the potential influence of advanced renal failure on calcium hemostasis.

Definition of the study variables

Risk factors' definition was made according to the most recent European Society of Cardiology (ESC) guidelines on hypertension, hyperlipidemia, and CV prevention: arterial hypertension (systolic BP [SBP] >140 bpm or diastolic BP >90 bpm), hyperlipidemia (LDL <1.8 mmol/L for high-risk patients; HDL <1.1 mmol/L and 1.0 mmol/L for women and men, respectively, and triglycerides >1.7 mmol/L), family history (MI or sudden cardiac death in an immediate male relative <55 years or female <65 years), and smoker (current smoker or those who quit smoking in the past 6 months). Body mass index (BMI) ≥30 kg/m^2 was used to define obesity. Type 2 DM was defined as established disease in patients treated with oral antidiabetic medication or insulin following initial treatment with oral antidiabetic therapy. Newly diagnosed diabetes was defined as having either one of the following criteria, based on the ESC guidelines on prediabetes and diabetes: fasting glucose of 7.0 mmol/L or nonfasting glucose 11.0 mmol/L in two separate samples, HbA1c >6.5%, or pathologic oral glucose tolerance test in patients with fasting glucose over 6.5 mmol/L without previously known or treated diabetes.

Myocardial perfusion single-photon emission computed tomography imaging

Myocardial SPECT study was performed in all patients using 1-day rest-stress protocol with Tc-99m sestamibi, using 15 mCi for the rest and 25 mCi for the stress study. We used single-head gamma camera Siemens E-cam with Siemens Symbia E-cam dual-headed camera with large detector system, with quantitative gated and perfusion SPECT software package (Corridor 4DM-SPECT Invia software package for the quantification, review and reporting of cardiac perfusion and function, developed at the University of Michigan, USA). Patients were instructed to refrain from caffeine-containing beverages for at least 12 h, nitrates for 24 h, and beta-blockers for 48 h prior to the study. All patients underwent pharmacological stressing with dipyridamole. We used the 17-segment model for quantitative Bull's eye analysis of regional myocardial perfusion and function. Myocardial perfusion was assessed by 5-point score system (0 – normal radiotracer uptake; 1 – mild, 2 – moderate; 3 – severe hypoperfusion; and 4 – absent uptake). Semi-quantitative analysis of regional perfusion at rest and stress was performed using Summed Stress Score (SSS), Summed Rest Score (SRS), and Summed Difference Score (SDS), aimed to assess the presence and extent of myocardial ischemia. Scan abnormalities were defined as follows: SSS <4 – normal perfusion; 4–8 – mild; 9–13 – moderate; and >13 – severely abnormal scan and SDS <7 – mild (<10% of LV); SDS 7–10 – moderate (10%–15% of LV); SDS >10 – severe ischemia (>15% of LV). Any perfusion abnormality was defined as SDS >4 and/or SRS >4. Regional wall motion analysis was assessed by a 6-point scoring system at rest and stress (0 – normal wall motion, 1 – mild, 2 – moderate; 3 – severe hypokinesia, 4 – akinesia, and 5 – dyskinesia) using Wall Motion Score Index.

Coronary Calcium Score imaging

Nonenhanced, prospectively ECG gated scan was obtained by the use of a 128-slice CT scanner (Siemens Somatom Definition 128 AC+, single source) for CCS imaging. Image reconstruction was performed at 55% of the R-R interval with prospective gating usage. The total calcium score in the coronary arteries was measured as a sum of individual scores of the major coronary arteries using Agatston score. On the basis of the total calcium score, patients were placed into five categories, as previously reported: CCS 0 (no evidence of atherosclerosis), 1–10 Agatston score (insignificant CCS), 11–100 Agatston score (mild CCS), 101–400 Agatston score (moderate CCS), and CCS >401 Agatston score (severe CCS). Total CCS score and CCS score in each coronary artery were assessed. The interpreting radiologist was blinded to all clinical and laboratory data.

Statistical analysis

Statistical analysis was performed with the use of the IBM SPSS Statistics, statistical package version 18.0 (New York, US). Categorical variables were compared using Chi-square test and continuous variables using unpaired Student's *t*-test. Categorical values were expressed in percentages, continued as mean value ± standard deviation; multivariate forward step-wise logistic regression analysis was built in order to identify predictors associated independently with increased hs-CRP (>1 mg/L), the presence of silent myocardial ischemia, and coronary atherosclerosis. The analysis included inflammatory biomarker – hs-CRP – and clinical risk factors (age, sex, type 2 diabetes, hypertension, hyperlipidemia, hs-CRP, smoking, obesity, and family history of cardiac disease). The criterion for inclusion into the model was a univariate probability value of $P < 0.05$ and $P > 0.10$ for removal from the model. P <0.05 was considered statistically significant for all statistical tests.

Results

The studied population included 41 male (60.2%) and 27 female patients (39.7%), with a mean age of 64 ± 9 years

as shown in Table 1. The prevalence of traditional risk factors and laboratory findings is presented in Tables 1 and 2. All patients had an average of two risk factors. The traditional risk factors were distributed as follows: 76.4% had arterial hypertension; 67.6% had hyperlipidemia; 26.4% were smokers, 13.2% were obese, and 35.2% of the patients had a family history of coronary disease.

hs-CRP was > 1 mg/L in 39 patients. The mean value of hs-CRP was 1.76 mg/L. hs-CRP values significantly varied based on the smoking duration history ($P = 0.02$). Smokers had higher hs-CRP values compared to nonsmokers or previous smokers (2.45 ± 0.3 vs. 1.91 ± 0.2, $P < 0.01$) and the values were also higher in obese patients. There was no difference in the hs-CRP values among patients with and without hyperlipidemia, most probably due to the influence of high-dose statin intake on the hs-CRP values. hs-CRP values were also higher in diabetic patients and in females.

Clinical predictors for increased high-sensitivity C-reactive protein

Multivariate forward step-wise analysis for predictors of the presence of increased hs-CRP (>1 mg/L) included the following variables: age, gender, hypertension, dyslipidemia, type 2 diabetes, family history of CAD, smoking, obesity, waist circumference, and statin use. Independent predictors for increased hs-CRP were as follows: type 2 diabetes (odds ratio [OR]: 6.932; 95% confidence interval [CI]: 1.398–13.147; $P < 0.034$); LDL-cholesterol (OR: 5.446, 95% CI: 1.734–9.567; $P < 0.26$); and obesity (OR: 4.145, 95% CI: 1.214–7.471; $P < 0.01$) [Table 3]. Patients had an average of two risk factors. The hs-CRP values were higher in patients with more than two risk factors; however, this was not statistically significant (hs-CRP mean value 2.13 mg/L in patients with two risk factors vs. 2.21 mg/L in patients with more than two risk factors, $P = 0.023$).

Association between high-sensitivity C-reactive protein and Coronary Calcium Score

CCS score was assessed in a total of 168 coronary arteries in 56 patients. In 12 patients, CCS was not done due to technical reasons. Elevated calcium score (CCS >0) was found in 26 patients (46.4%). Seven patients had CCS between 10 and 99 (10.7%), 8 patients between 100 and 400 (14.2%), and 11 patients had severe CCS >400 (16.0%). Increased CCS was located in the left anterior descending artery (LAD) in 16 patients, in the circumflex artery in 7 patients, and in the right coronary artery in 9 patients. Mean value of the CCS was 106 ± 42. hs-CRP >1 mg/L was noted in 18 patients with CCS >0, and the value increased with the extensity of CCS. Patients with normal MPI scan had an average CCS score of 22 ± 18. Patients with moderate and severe ischemia had CCS score of 367 ± 112. The prevalence of increased Coronary Calcium Score detected increased with the number of risk factors including age, obesity, hypertension, dyslipidemia, diabetes, hs-CRP >1 mg/L, smoking, and family history, which is shown in Table 4.

Multivariate regression analysis (forward stepwise) demonstrated the following parameters as independent predictors for the presence of increased CCS (CCS >0 AU): LDL cholesterol (OR: 2.891, 95% CI: 1.131–5.192; $P = 0.001$); age >70 years (OR: 2.568, 95% CI: 1.050–4.920; $P < 0.031$), and smoking (OR: 1.931, 95% CI: 1.214–3.238; $P < 0.02$) [Table 5].

Association between high-sensitivity C-reactive protein and myocardial ischemia

Thirty patients (44.1%) had abnormal MPI scan results. Mild ischemia (SDS <7) was noted in 11 patients, moderate ischemia (SDS 7.10) in 10 patients, and severe ischemia (SDS >10) in 6 patients. Three patients had fixed mild perfusion defects in <2 myocardial segments. Eleven patients with moderate and severe ischemia had CCS >100 AU (66.6%) and the other five patients had CCS = 0. Patients with moderate and severe myocardial ischemia showed higher hs.CRP values compared to patients with normal MPI findings.

Multivariate regression analysis (forward stepwise) showed the following parameters as independent predictors for the presence of increased CCS (CCS >0): myocardial

Table 2: Clinical characteristics of the study population

	Number of patients (68), *n* (%)
Hypertension	52 (76.4)
Hyperlipidemia	46 (67.6)
DM type 2	55 (80.8)
Smoking	18 (26.4)
Obesity	9 (13.2)
Family history	24 (35.2)

DM: Diabetes mellitus

Table 3: Multivariable regression forward step-wise analysis for prediction of increased high-sensitivity C-reactive protein which included age, gender, hypertension, low-density lipoprotein >1.8 mmol/l, diabetes, smoking, obesity, family history, and Coronary Calcium Score >0

	P	OR (95% CI)
Sex	0.817	1.089 (0.526-2.251)
Age	0.061	1.025 (0.471-1.913)
BMI ≧30	0.01	4.145 (1.214-7.471)
Hypertension	0.079	1.972 (1.050-2.352)
LDL>1.8 mmol/l	0.001	5.446 (1.734-9.567)
DM type 2	0.001	6.932 (1.398-13.147)
Smoking	0.287	0.979 (0.522-1.837)
Family history of CAD	0.076	0.539 (0.273-1.067)

Age: Men >45 years, women >55 years. CAD: Coronary artery disease, DM: Diabetes mellitus, BMI: Body mass index, LDL: Low-density lipoprotein, OR: Odds ratio, CI: Confidence interval

Table 4: Prevalence of increased Coronary Calcium Score detected by multisliced coronary computed tomography with a number of risk factors including age, obesity, hypertension, dyslipidemia, diabetes, high-sensitivity C-reactive protein >1 mg/L, smoking, and family history

Risk factor number	Total number of patients (%)	Number of patients with increased Coronary Calcium Score	*P*	OR (95% CI)
<2	26 (38.2)	7 (10.2)	<0.001	7.013 (2.760-15.276)
≧2	42 (61.7)	19 (27.9)		

OR: Odds ratio, CI: Confidence interval

ischemia type 2 diabetes (OR: 5.112, 95% CI: 1.078–11.187; $P = 0.001$); LDL-cholesterol (OR: 4.446, 95% CI: 1.454–7.597; $P < 0.001$); and hs-CRP (OR: 3.135, 95% CI: 1.398–6.951; $P < 0.01$) [Table 6]. Twelve patients who did not have CCS evaluated had normal MPI scan results and three patients had mild myocardial ischemia (SDS <7).

Discussion

It is becoming clear that the pathogenesis of atherosclerotic plaque formation involves not only vascular wall lipid accumulation, but also low-grade chronic inflammation and endothelial dysfunction.[12] hs-CRP is an acute-phase protein that is increased rapidly in response to infection or injury and plays an important role in the development and progression of inflammation. It is the most widely studied inflammatory protein that has gained most clinical attention to date. hs-CRP has been recognized to be an independent predictor of CV events, which also improves CV risk stratification.[12,13] Sophisticated CV risk scores, such as Reynolds score which includes hs-CRP, are based on the evidence of the prognostic value of this marker. Ridker was a pioneer with his work who confirmed the hypothesis that hs-CRP is both a marker of inflammation and a predictor of increased CV risk.[14] From a number of studies, it is clear that an association exists between increased hs-CRP levels and greater CV risk (studies such as JUPITER, MESA).[15,16]

There is an ongoing debate whether hs-CRP is merely a marker of inflammation or whether it contributes to the development of atherosclerosis. It has been shown that hs-CRP increases the number of monocytes into atherosclerotic plaques which induce endothelial dysfunction. The hs-CRP also increases the expression of vascular endothelial plasminogen activator inhibitor-1 and reduces LDL uptake by macrophages.[14] Plasma hs-CRP levels have an influence on plaque inflammation severity and enhance plaque formation. Inflammation links metabolic syndrome and insulin resistance with atherosclerosis, increasing the risk for the development of type 2 diabetes.[17] hs-CRP induces oxidative stress and promotes angiotensin activity, which stimulates vascular wall remodeling. In addition, it activates the complement cascade and prothrombotic state. Plasma levels of hs-CRP increase with increasing CAD severity and extensity and can serve as a predictor of CV events with 2-fold increase in the risk of stroke and a 3-fold increase in the risk of myocardial infarction.[18]

Table 5: Multivariate logistic regression (forward stepwise) analysis for predictors of increased Coronary Calcium Score which included age, gender, hypertension, low-density lipoprotein >1.8 mmol/L, diabetes, smoking, obesity, family history, and high-sensitivity C-reactive protein >1 mg/L

	P	OR (95% CI)
Sex	0.817	1.089 (0.526-1.951)
Age	0.001	2.568 (1.471-17.164)
BMI ≥30	0.089	0.564 (0.313-2.016)
Hypertension	0.129	1.972 (1.050-3.352)
LDL >1.8 mmol/L	0.001	2.891 (0.950-5.554)
DM type 2	0.081	1.901 (0.247-3.771)
Smoking	0.001	1.931 (0.522-4.837)
Family history of CAD	0.076	0.539 (0.273-1.067)

Age: men >45 years, women >55 years. CAD: Coronary artery disease, DM: Diabetes mellitus, BMI: Body mass index, LDL: Low-density lipoprotein, OR: Odds ratio, CI: Confidence interval

Table 6: Multivariate logistic (forward stepwise) regression analysis for predictors of the presence of single-photon emission computed tomography myocardial ischemia which included age, gender, hypertension, low-density lipoprotein >1.8 mmol/L, diabetes, smoking, obesity, family history, high-sensitivity C-reactive protein >1 mg/L, and Coronary Calcium Score >0 Agatston unit

	P	OR (95% CI)
Sex	0.817	1.089 (0.526-3.251)
Age	0.061	1.025 (0.471-4164)
BMI ≧30	0.078	1.564 (0.313-5.016)
Hypertension	0.129	0.972 (0.650-5.352)
LDL >1.8 mmol/L	0.001	4.446 (2.550-9.554)
DM type 2	0.001	5.112 (1.247-11.771)
Smoking	0.287	0.979 (0.522-1.837)
Family history of CAD	0.076	0.539 (0.273-1.067)
Hs-CPR >1 mg/L	0.01	3.135 (1.401-6.210)

Age: Men >45 years, women >55 years. CAD: Coronary artery disease, DM: Diabetes mellitus, BMI: Body mass index, LDL: Low-density lipoprotein, OR: Odds ratio, CI: Confidence interval, hs-CRP: High-sensitivity C-reactive protein

The commonly used models for prediction of CV risk (SCORE, Framingham, and PROCAM) are based on traditional risk factors such as age, gender, smoking,

BP, cholesterol values, or type 2 diabetes. There are well-known inferiorities of those models to predict CV events. Approximately 40% of patients with coronary events have no or only one risk factor. Over one-third of patients who die due to CVD have cholesterol levels within the normal limits. These facts urge the scientific and clinical community to search for new risk factors which will aid toward reclassifying patient's risk. However, so far, there are no specific advantages in hs-CRP reductions that may prevent clinical events and prognosis compared to traditional risk factor management. Evaluation of inflammatory biomarkers and subclinical atherosclerosis with CCS improves individual risk assessment and reclassifies patient's risk.

Our study shows relatively high prevalence of silent myocardial ischemia and subclinical atherosclerosis in an asymptomatic high-risk population. Multivariate regression analysis showed hs-CRP as an independent predictor only for myocardial ischemia and not for the CCS. hs-CRP as an inflammatory marker was not shown to have independent incremental value on CCS presence and extensity in this study population. Inflammatory activity expressed as hs-CRP levels might have a different impact on myocardial ischemia as a functional expression of CAD significance.[19,20] Our results also suggest that calcification may be less likely to reflect inflammation exclusively. Multislice CT-detected calcification may predominantly be a marker for stable atherosclerotic plaque and present only an indirect marker for the presence of uncalcified plaques, which may be more likely markers for future cardiac events. hs-CRP levels increased with the severity of myocardial ischemia, despite the use of statins. Our study results show that hs-CRP and CCS assessment may identify asymptomatic high-risk patients who may be candidates for myocardial ischemia screening. Medical therapy was intensified in patients with high CCS and increased hs-CRP values.

Based on the literature, hs-CRP is a marker of inflammation and CCS is a marker of atherosclerosis. Both markers are of different pathologic processes which provide individual information regarding CV risk. CCS is a direct measure of atherosclerosis burden as a cumulative effect of all risk factors on the vessel wall. There are conflicting study results with regard to the association of hs-CRP and CCS.[21] In the study of Hosseinsabet *et al*., hs-CRP was not correlated with CCS. The relation between hs-CRP and clinical events might not be associated with atherosclerotic burden extension. Redberg *et al.* also did not find an association between hs-CRP and CCS in postmenopausal women. Assessment of atherosclerosis by coronary calcium screening and inflammation activity with hs-CRP independently predicts coronary events and all-cause mortality in individuals without known CAD based on the Heinz Nixdorf Recall Study.[22] The risk of coronary events increased with increasing CCS score and hs-CRP values. Both hs-CRP and CCS added incremental and independent prognostic information to the Framingham Risk Score. Coronary risk was predicted mainly by CCS, whereas hs-CRP improved risk prediction in patients with low CCS scores. The clinical advantage of using these two distinct markers which measure atherosclerosis and inflammation burden is the ability to identify individuals with highest and lowest CV risk with improved accuracy compared to traditional risk factors. Coronary Calcium Score in the study by Redberg *et al*. was a stronger predictor for coronary events compared to hs-CRP. Möhlenkamp *et al.*, however, reported that individuals who have no or a very low values of CCS and hs-CRP >3.0 mg/L had more than 4.5 times increased risk for coronary events compared to those with lower hs-CRP values.[23] JUPITER-like cohort of the Multi-Ethnic Study of Atherosclerosis (MESA) followed participants for a median of 5.8 years, who had normal LDL-cholesterol levels and elevated hs-CRP (>2 mg/L). Throughout the follow-up period, 2/3rd of all coronary heart disease events occurred in patients with a CCS score >100. Latest research data from the MESA study on 6751 patients showed that the addition of CCS score to global risk assessment is associated with significantly improved risk classification in individuals with metabolic syndrome and diabetes, confirming the clinical value of CCS score in risk assessment in this population.[24] According to those study results, asymptomatic patients with a CCS score of 0 can be treated less aggressively with lifestyle changes. Studies of CCS might permit differentiation of factors associated with coronary atherosclerosis from those related to coronary thrombosis. CCS assessment has small repeat testing variability, established and consistent thresholds of risk in different age and gender populations, and higher costs compared to hs-CRP assessment. However, hs-CRP values vary by gender and race. Multivariate regression analysis in this study showed LDL-cholesterol, age >70 years, and smoking as independent predictors for increased CCS (>0 AU). This study did not show hs-CRP to be an independent predictor for increased CCS, although hs-CRP values increased with the extensity of CCS.

A number of studies and meta-analyses using SPECT imaging have established the prognostic values of myocardial ischemia severity and extensity. In fact, lower levels of CRP have been reported in patients with normal perfusion scan compared to patients with abnormal SPECT scans and myocardial ischemia.[25] Prognostic value of MPI and CCS was also established in our previous studies.[26,27] There is an ongoing debate whether ischemia-based management in both symptomatic and asymptomatic patients with suspected or established stable CAD could change prognosis. Several studies such as COURAGE and BARI 2D have not shown any prognostic advantages of invasive management of patients with stable CAD.[28] However, it is expected that, from the large ongoing ISCHEMIA trials, insights will be given into these issues.[28] Keeping in mind the association between

hs-CRP in patients with abnormal perfusion scan and its role in inflammation and atherosclerosis, CRP measurement can improve individual selection of the patients with an increased risk for CAD who might benefit for ischemia detection. The predictive value of hs-CRP on clinical outcomes in patients with diabetes was previously reported by Bosevski *et al.*[29,30]

We are entering the new era where targeting inflammation will be the point of care of patients not only with cardiovascular disease. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study is the first report showing that the decrease in inflammation independently of cholesterol levels reduces CV risk. The study gives very important clinical massage implicating that cardiovascular risk can be reduced not only by treating to the target cholesterol levels, but also targeting and treating inflammatory markers.[31] The study message is an entirely new treatment approach which is targeting inflammation. This may significantly improve outcomes for individual high-risk patients.

Study limitations

This is a cross-sectional study. Atherosclerosis in vascular beds other than the coronary arteries could also influence the level of hs-CRP. The use of medications which include high dose of statins, angiotensin-converting enzyme inhibitors, and/or angiotensin-receptor blockers may have an influence on our study results due to their pleiotropic or anti-inflammatory effects.

Conclusion

hs-CRP is an independent predictor for silent myocardial ischemia as determined in this study by MPI. LDL-cholesterol, age, and smoking were independent predictors for increased Coronary Calcium Score as marker for coronary atherosclerosis burden. It suggests that hs-CRP might be a measure of athero-inflammatory process with indirect functional repercussion on the myocardium and not exclusively an index of the extent of coronary atherosclerosis burden. This marker may improve the selection of asymptomatic high-risk patients who may benefit for SPECT myocardial ischemia screening. This approach may redefine individual risk evaluation and intensify primary prevention management in high-risk patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Stoll G, Bendszus M. Inflammation and atherosclerosis: Novel insights into plaque formation and destabilization. Stroke 2006;37:1923-32.
2. Fan J, Watanabe T. Inflammatory reactions in the pathogenesis of atherosclerosis. J Atheroscler Thromb 2003;10:63-71.
3. Authors/Task Force Members, Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, *et al.* 2016 European Guidelines on Cardiovascular disease prevention in clinical practice: The sixth joint task force of the European Society of Cardiology and Other Societies on Cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur J Prev Cardiol 2016;23:NP1-96.
4. Habib SS, Kurdi MI, Al Aseri Z, Suriya MO. CRP levels are higher in patients with ST elevation than non-ST elevation acute coronary syndrome. Arq Bras Cardiol 2011;96:13-7.
5. Ridker PM. C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: Moving an inflammatory hypothesis toward consensus. J Am Coll Cardiol 2007;49:2129-38.
6. Cook NR, Buring JE, Ridker PM. The effect of including C-reactive protein in cardiovascular risk prediction models for women. Ann Intern Med 2006;145:21-9.
7. Hunt ME, O'Malley PG, Vernalis MN, Feuerstein IM, Taylor AJ. C-reactive protein is not associated with the presence or extent of calcified subclinical atherosclerosis. Am Heart J 2001;141:206-10.
8. Bourque JM, Beller GA. Stress myocardial perfusion imaging for assessing prognosis: An update. JACC Cardiovasc Imaging 2011;4:1305-19.
9. Seyedian SM, Ahmadi F, Dabagh R, Davoodzadeh H. Relationship between high-sensitivity C-reactive protein serum levels and the severity of coronary artery stenosis in patients with coronary artery disease. ARYA Atheroscler 2016;12:231-7.
10. Roivainen M, Viik-Kajander M, Palosuo T, Toivanen P, Leinonen M, Saikku P, *et al.* Infections, inflammation, and the risk of coronary heart disease. Circulation 2000;101:252-7.
11. Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple risk factor intervention trial. Am J Epidemiol 1996;144:537-47.
12. Hosseinsabet A, Mohebbi A, Almasi A. C-reactive protein and Coronary Calcium Score association in coronary artery disease. Cardiol J 2008;15:431-6.
13. Mahabadi AA, Möhlenkamp S, Moebus S, Dragano N, Kälsch H, Bauer M, *et al.* The heinz nixdorf recall study and its potential impact on the adoption of atherosclerosis imaging in European primary prevention guidelines. Curr Atheroscler Rep 2011;13:367-72.
14. Redberg RF, Rifai N, Gee L, Ridker PM. Lack of association of C-reactive protein and coronary calcium by electron beam computed tomography in postmenopausal women: Implications for coronary artery disease screening. J Am Coll Cardiol 2000;36:39-43.
15. Blaha MJ, Budoff MJ, DeFilippis AP, Blankstein R, Rivera JJ, Agatston A, *et al.* Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: Implications for the JUPITER population from MESA, a population-based cohort study. Lancet 2011;378:684-92.
16. Malik S, Zhao Y, Budoff M, Nasir K, Blumenthal RS, Bertoni AG, *et al.* Coronary artery calcium score for long-term risk classification in individuals with type 2 diabetes and metabolic syndrome from the multi-ethnic study of atherosclerosis. JAMA Cardiol 2017;2:1332-40.
17. Paoletti R, Bolego C, Poli A, Cignarella A. Metabolic Syndrome, Inflammation and Atherosclerosis. Vasc Health Risk Manag 2006;2:145-52.
18. Razban MM, Eslami M, Bagherzadeh A. The relationship

between serum levels of hs-CRP and coronary lesion severity. Clujul Med 2016;89:352-64.
19. Shrivastava AK, Singh HV, Raizada A, Singh SK. C-reactive protein, inflammation and coronary heart disease. The Egyptian Heart Journal 2015;67:89-97.
20. Ridker PM. Inflammation, C-Reactive Protein, and Cardiovascular Disease. Circulation Research 2014;114:594-5.
21. Hosseinsabet A, Mohebbi A, Almasi A. Association between C-reactive protein and coronary calcium score in coronary artery disease. Cardiovasc J Afr 2009;20:107-11.
22. Lehmann N, Erbel R, Mahabadi AA, Rauwolf M, Möhlenkamp S, Moebus S, *et al*. Value of progression of coronary artery calcification for risk prediction of coronary and cardiovascular events. Result of the HNR study (Heinz Nixdorf Recall). Circulation 2018;137:665-79.
23. Möhlenkamp S, Lehmann N, Moebus S, Schmermund A, Dragano N, Stang A, *et al*. Heinz Nixdorf recall study investigators. Quantification of coronary atherosclerosis and inflammation to predict coronary events and all-cause mortality. J Am Coll Cardiol 2011;57:1455-64.
24. Blaha MJ, Rivera JJ, Budoff MJ, Blankstein R, Agatston A, O'Leary DH, *et al*. Association Between Obesity, High-Sensitivity C-Reactive Protein >=2 mg/L, and Subclinical Atherosclerosis: Implications of JUPITER from the Multi-Ethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol 2011;3:1430-8.
25. Rashidinejad H, Moazanzadeh M, Mirshekarpoor H, Ebrahim F. The relationship between HS-CRP serum levels with the results of cardiac perfusion SPECT imaging in patients with suspected coronary artery disease. Asian Journal of Biomedical and Pharmaceutical Sciences, 2015;5:30-3.
26. Mitevska IP, Baneva N, Srbinovska E, Stojanovska L, Apostolopoulos V, Bosevski M, *et al.* Prognostic implications of myocardial perfusion imaging and Coronary Calcium Score in a macedonian cohort of asymptomatic patients with type 2 diabetes. Diab Vasc Dis Res 2017;14:285-94.
27. Peovska Mitevska I, Davceva Pavlovska J, Srbinovska E, Bosevski M, Zdravkovska M, Pop Gorceva D, *et al.* Ischaemia-driven optimal therapeutic approach in asymptomatic patients with high cardiovascular risk: The value of clinical, laboratory and myocardial SPECT imaging findings. Pril (Makedon Akad Nauk Umet Odd Med Nauki) 2014;35:141-8.
28. Phillips LM, Hachamovitch R, Berman DS, Iskandrian AE, Min JK, Picard MH, *et al*. Lessons learned from MPI and physiologic testing in randomized trials of stable ischemic heart disease: COURAGE, BARI 2D, FAME, and ISCHEMIA. J Nucl Cardiol 2013;20:969-75.
29. Bosevski M, Bosevska G, Stojanovska L, Apostolopoulos V. CRP and fibrinogen imply clinical outcome of patients with type-2 diabetes and coronary artery disease. Acta Biochim Biophys Sin (Shanghai) 2017;49:284-5.
30. Bosevski M, Stojanovska L, Apostolopoulos V. Inflammatory biomarkers: Impact for diabetes and diabetic vascular disease. Acta Biochim Biophys Sin (Shanghai) 2015;47:1029-31.
31. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, *et al.* Anti-inflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119-31.