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Role of C-reactive Protein in Peripheral Arterial Disease

Dr. Robert Skopec Ibaram

Abstract:

Objective: To review the role of elevated C - reactive protein (CRP) as a marker for predicting the development of Peripheral Arterial Disease (PAD). ***Methods:*** An online search was conducted using the most trusted medical data base PubMed and the articles published in peer-reviewed journals within the last 5 years (from the year 2005 to date) to collect evidence about the association of C-reactive protein with Peripheral Arterial Disease, using keywords like C-reactive protein, hs-C-reactive protein, inflammation, atherogenesis, peripheral arterial disease and their combinations. Out of 240 articles shown during online search on PubMed, only 17 articles related to the role of CRP and High sensitivity CRP (hs-CRP) as a marker in PAD. ***Results:*** 17 articles based on the role of CRP and High sensitivity CRP (hs-CRP) as a marker in PAD were studied and evaluated thoroughly working on their study design and outcomes. Almost all the 17 studies showed strong association hs-CRP with PAD. The results are described in the form of a table. ***Conclusion:*** CRP seems to be a marker of severity of PAD and it may serve as a strong prognostic indicator.

Keywords: C-reactive protein, hs-C-reactive protein, inflammation, atherogenesis, peripheral arterial disease

Introduction

Peripheral arterial disease is a common cause of cardiovascular morbidity and an independent predictor of cardiovascular mortality.[1] Cardiovascular Disease (CVD) remains the leading cause of death in most developed countries, with approximately one million Americans annually dying from CVD and more than 19 million deaths per year worldwide from atherosclerotic CVD.

The role of Inflammation: There is considerable interest in the correlation between atherosclerotic plaque burden and elevated CRP - an inflammatory marker in plasma considering that the traditional risk factors do not totally account for the PAD. Moreover, inflammation may predispose to plaque vulnerability promoting sudden expansion, rupture and release of distal emboli promoting vascular occlusion. CRP has been utilized over the years in monitoring many diseases and recently a new use for CRP has gained momentum based on observations that minor elevations in CRP are predictive of cardiovascular events.[2]

C Reactive Protein: It is a pentameric protein discovered in 1930 by Tillett and Francis.[3] It is produced when cytokines especially IL6, IL1 and TNFa stimulate hepatocytes in response to tissue damage or infection.[3] In a study by Ridker et al.,[4] they found that of 11 atherothrombotic biomarkers assessed at baseline, CRP and the total cholesterol–HDL-C ratio were the strongest independent predictors of development of peripheral arterial disease. C-reactive protein provided additive prognostic information over standard lipid measures.[4]

However, traditional CRP tests designed to monitor inflammation were found to have poor sensitivity at lower ranges, leading to the development of High sensitivity CRP (hs-CRP).[5]

Hs-CRP has been demonstrated by several large-scale prospective studies to be a strong independent predictor of future myocardial infarction and stroke among apparently healthy men and women and that the addition of HSCRP to standard lipid screening may improve global risk prediction among those with high as well as low cholesterol levels.[4] Moreover, the Physicians' Health Study showed a strong link between hs-CRP and peripheral vascular disease, independently of all other risk factors, including heart disease. Several prospective epidemiological studies have demonstrated a consistent relationship between higher C-reactive protein (CRP) levels and increased risk of cardiovascular (CV) events, including myocardial infarction, stroke, and CV death. Despite these robust epidemiological data, the mechanisms relating CRP to incident CV events are unclear.[6]

Methods

An online search was conducted using the most trusted medical data base PubMed and the articles published in peer-reviewed journals within the last 5 years (from the year 2005 to date) to collect evidence about the association of C-reactive protein with Peripheral Arterial Disease, using keywords like C-reactive protein, hs-C-reactive protein, inflammation, atherogenesis, peripheral arterial disease and their combinations. The articles specifically demonstrating the relationship or link between inflammation, CRP and PAD were included and all others were excluded. 240 articles were shown during online search on PubMed, out of which only 17 articles matched the inclusion criteria.

Results

Authors	Year	Title	Study Design	Outcome
Singh et al. [7]	2017	Systematic Review and Meta-Analysis of the Association Between C-Reactive Protein and Major Cardiovascular Events in Patients with Peripheral Artery Disease.	Systematic review and meta-analysis	CRP is predictive of major CV events in PAD patients.
Vonbank et al. [8]	2016	C-reactive protein significantly predicts cardiovascular events both in peripheral arterial disease patients with and in peripheral arterial disease patients without the metabolic syndrome	Case series study	CRP significantly predicts CV risk in PAD patients.
Igari et al. [9]	2016	Relationship of Inflammatory Biomarkers with Severity of Peripheral Arterial Disease	Retrospective clinical study	Pentrexin family including hs-CRP and Pentrexin 3 may be considered as prognostic marker for the severity of PAD.
Kumakura et al. [10]	2015	Hs-CRP, lipoprotein (a) and homocysteine are risk factors for coronary artery disease in japanese patients with peripheral arterial disease	Clinical trial	Diabetes, hs-CRP, Lp(a), homocysteine and lipid abnormalities are critical risk factors for CAD in Japanese patients with PAD.
Stone et al. [11]	2014	C-reactive protein and brain natriuretic peptide as predictors of adverse events after lower extremity endovascular revascularization	Cross sectional study	Elevated levels of hsCRP and BNP are associated with late cardiovascular events.
Sung et al. [12]	2014	C-reactive protein and subclinical cardiovascular disease among African-Americans: (the Jackson Heart Study)	Cohort	Significant associations were revealed between CRP and AVC and PAD.
Van Wijk et al. [13]	2013	C-reactive protein, fatal and nonfatal coronary artery disease, stroke, and peripheralartery disease in the prospective EPIC-Norfolk cohort study	Cohort	CRP was associated with fatal and nonfatal CAD events, as well as nonfatal PAD events.
Bosevski et al. [14]	2013	Influence of fibrinogen and C-RP on progression of peripheral arterial disease in type 2 diabetes: a preliminary report	cohort prospective study	Plasma determination of fibrinogen and CRP may have a clinical implication in the process of progression of PAD in T2D population.
Ishii et al. [15]	2013	Serum albumin and C-reactive protein levels predict clinical outcome in hemodialysis patients undergoing endovascular therapy for peripheral artery disease	Cohort	Lower albumin and elevated CRP levels could strongly predict major adverse events and major adverse limb events after EVT in the patients on hemodialysis.
Gomez-Marcos et al. [16]	2012	Relationships between high-sensitive C-reactive protein and markers of arterial stiffness in hypertensive patients. Differences by sex	Case-series study	HS-CRP turned out to be positively correlated to carotid intima-media thickness in men and negatively correlated to central central augmentation index in women.
Chen et al. [17]	2012	Risk factors for peripheral arterial disease among patients with chronic kidney disease	Cross-sectional	Inflammation, prothrombotic state, oxidative stress, insulin resistance and cystatin C seemed to be associated with an increased prevalence of PAD in patients with CKD.
Criqui et al. [18]	2010	Biomarkers in Peripheral Arterial Disease Patients and Near and Longer Term Mortality	Cohort	Hs-CRP turned out to be a strong predictor of short-term mortality in the PAD patients.
Ishii et al. [19]	2010	Prognostic values of C-reactive protein levels on clinical outcome after endovascular therapy in hemodialysis patients with peripheral artery disease	Cohort	Raised preprocedural serum CRP levels seemed to be associated with intervention or above-ankle amputation of the limb index and any-cause death after endovascular therapy in hemodialysis patients with peripheral artery disease.
Momiyama et al. [20]	2009	Prognostic value of plasma high-sensitivity C-reactive protein levels in Japanese patients with stable coronary artery disease: the Japan NCVC-Collaborative Inflammation Cohort (JNIC) Study	Cohort study	Raised hsCRP is associated with a significantly increased risk for further cardiovascular events.
Bo et al. [21]	2009	High-sensitivity C-reactive protein is not independently associated with peripheralsubclinical atherosclerosis	Cross sectional	hsCRP has limited predictive role in subclinical atherosclerosis.
De Haro et al. [22]	2008	Relationship between the plasma concentration of C-reactive protein and severity of peripheral arterial disease	Cross sectional study	CRP levels are associated with not only the presence of atherosclerosis but also with its chronological clinical severity.

Hogh et al. [23]	2008	C-reactive protein predicts future arterial and cardiovascular events in patients with symptomatic peripheral arterial disease	Clinical trial	Baseline levels of hsCRP are associated with future arterial events in symptomatic peripheral arterial disease patients but cannot stand alone as a predictive tool.
Mullenix et al. [24]	2007	C-reactive protein level and traditional vascular risk factors in the prediction of carotid stenosis	Cohort study	CRP is statistically significant marker of carotid stenosis and may be a useful adjunct to accurate global vascular risk assessment.
Shankar et al. [25]	2007	Association between C-reactive protein level and peripheral arterial disease among US adults without cardiovascular disease, diabetes, or hypertension	Cross-sectional study	Higher CRP levels are associated with PAD among US adults free of CVD, diabetes, and hypertension.
Abdellaoui & Al-Khaffaf [5]	2007	C-reactive protein (CRP) as a marker in peripheral vascular disease	Review	CRP appears to be a strong predictor and marker of severity of PVD.
Vainas et al. [26]	2005	C-reactive protein in peripheral arterial disease: relation to severity of the disease and to future cardiovascular events	Prospective observational study	hsCRP is associated with the severity of PAD.

Discussion

C-reactive protein (CRP) is an acute phase pentameric protein which is secreted by liver in response to inflammatory processes occurring in the body. The level of CRP in blood increases rapidly in response to inflammation, infection and trauma, and decreases as soon as the condition resolves.[27] It is considered as a part of immune system as it activates complement system and functions as an opsonin for a variety of pathogens. Peripheral arterial disease (PAD) is a circulatory problem where narrowed blood vessels due to atherosclerosis reduce blood flow to the extremities. Several large scaled studies have demonstrated a close link between inflammation and PAD.[28,29] Similarly, several prospective studies have demonstrated significant association between CRP and PAD.[12,13]

Recently, Sung et al.,[12] conducted a population-based cohort study by recruiting participants from Jackson Heart Study. They reported significant relationship between CRP and atherosclerosis among middle-aged and elderly African Americans. They also demonstrated as "*the higher the CRP, the more chances of developing AVC and ankle-brachial index (ABI)-defined PAD*" suggesting that CRP reflects the burden of atherosclerosis among African Americans. However, cross-sectional design and self-reporting of CVD indicate the need of large prospective and randomized studies to establish the exact relationship between CRP and atherosclerosis. Similarly, Van Wijk et al.,[13] conducted a study including 18,450 participants from EPIC-Norfolk cohort and reported that CRP was associated with fatal and nonfatal CAD events, strokes and PAD events with predominance of fatal CAD events. In short, they reported strong and independent association between CRP and PAD outcomes. Although this study is with a great strength in terms of our topic of discussion; however, non-atherosclerotic events and use of statins might have affected the CVD outcomes.

Raised CRP has also been reported in the patients with PAD and co-morbidities like T2D and kidney problems. Bosevski et al.,[14] conducted a prospective cohort study including 62 patients with PAD and T2D (Age: 60.28 ± 27 years) in order to demonstrate role of inflammatory biomarkers in the pathogenesis of atherosclerosis in the patients with T2D. They reported that plasma determination of fibrinogen ($p = 0.007$) and CRP ($p = 0.037$) in terms of ABI measurements may predict the progression of PAD in the patients with T2D. Small sample size and preliminary nature of this study suggest large prospective studies in future. Similarly, Chen et al.,[17] conducted a cross-sectional study including 3758 patients with chronic kidney disease recruited from the chronic renal insufficiency cohort (CRIC) study in order to determine association between novel risk factors and prevalent PAD among patients with CKD. They reported hs-CRP (along with many other risk factors) as significantly associated with higher odds of PAD.

Gomez-Marcos et al.,[16] carried out case series study on 258 patients with hypertension and without any antecedent cardiac issue or diabetes in order to determine the relationship between hs-CRP and arterial stiffness. They used Nephelometry, OMRON model M10 sphygmomanometer, Sonosite Micromax ultrasound unit and SphygmoCor system for the measurement of hs-CRP, ambulatory blood pressure, carotid intima-media thickness (IMT) measurements and central/ peripheral augmentation index (AIx) respectively. They reported positive correlation between CRP and carotid IMT in men and negative correlation in women. However, this study cannot be applied to general population as it was based on cross sectional design and consecutive sampling. Similarly, Criqui et al.[18] and Ishii et al.[15&19] reported that hs-CRP turns out to be a strong predictor of short-term mortality in the PAD patients and in the patients on hemodialysis and PAD.

In contrast, Syvanen et al.[30] conducted a population survey in Finland to determine the correlation of hs-CRP and ABI. They demonstrated that although hsCRP was correlated to the measures of obesity; however, it did not seem to be a suitable screening method for PAD. Thus, CRP or hs-CRP is still a controversial mediator for being a prognostic factor for PAD. Although this study includes all the articles based on the relationship of CRP with PAD published from 2005 to 2014; however, the evidence of this relationship dates back when Ridhker et al.,[31] conducted a prospective case-control study revealing that baseline levels of CRP predict future risk of developing symptomatic PAD.

In short, CRP seems to be associated with PAD and its progression and may be a prognostic factor for the same disease. However, as reviewed by Krishna et al.,[32] single biomarker cannot be enough

for the prognosis of PAD as it is a multi-factorial condition. Also, it has been reported that higher values of CRP in the patients with PAD indicate higher risk of CV events.[7,8]

Conclusion

CRP especially hs-CRP turns out to be associated with PAD. However, there is dire need of large prospective randomized studies to establish a clear relationship between CRP and PAD and to develop guidelines for CRP to be as a prognostic factor in the patients with CVD.

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