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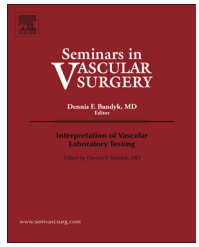

Inflammatory biomarkers in peripheral arterial disease

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ARTICLE INFO

ABSTRACT

Biochemical markers have the potential to aid the vascular specialist in many ways. On a daily basis, we rely on such markers as D-dimer to help exclude thromboembolic disease and thus limit low-probability ultrasound imaging. Additionally, we use troponin levels to determine myocardial events perioperatively. During the past decade, use of the inflammatory marker C-reactive protein has been recommended by the American Heart Association to further stratify patient cardiovascular risk, and has been studied more extensively in patients with peripheral vascular disease. This review details clinical information published during the past several decades on the application of serum C-reactive protein levels in peripheral arterial disease patients in correlation with disease severity and likelihood of future cardiovascular events, including recent predictive models.

1. Introduction

Inflammation within the arterial circulation has been thought to be a contributing factor to development of atherosclerotic plaques. Attempts at quantifying the degree of ongoing inflammation have been pursued in the last several decades through measurement of serum biochemical markers. The most widely studied and reported biomarker is C-reactive protein (CRP) [1,2]. Although studied most extensively in the cardiovascular literature, this review discusses the available data on CRP levels in the subgroup of patients with peripheral arterial disease (PAD).

2. Population-based studies

When comparing patients with and without peripheral vascular disease, elevated CRP levels were found more frequently in patients with peripheral vascular disease who were free of diabetes or hypertension [1]. In a study of >3,000 patients, Pande et al [1] reported an incidence of PAD in approximately 5% of patients. The PAD patient was older, more frequently hypertensive, and reported a history of cardiac and renal disease. Those with PAD, defined by ankle brachial index (ABI) ≤0.9, were statistically more likely to have a serum CRP level >3 mg/dL (54% *v* 40%), and a significantly higher ($P < .02$) mean CRP level of 7.5 ± 1.3 mg/dL versus 4.4 ± 0.2 mg/dL. This report also emphasized the importance of insulin resistance as an independent factor in PAD and attenuates the association of inflammation as measured by CRP in the PAD cohort.

In a larger study of >13,000 patients, Ridker et al [2] measured multiple inflammatory markers to assess their association with PAD, including von Willebrand factor, fibrinogen, D-dimer, factor VII, factor VIII, plasminogen activator inhibitor-1, tissue plasminogen activator, β-thromboglobulin, CRP, and white blood cell count. Although fibrinogen levels were found to have the highest odds ratio in predicting

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http://dx.doi.org/10.1053/j.semvascsurg.2015.01.009
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patients with PAD, CRP also demonstrated a statistically significant correlation of risk for PAD compared with those without PAD. In addition, a small prospective cohort of nearly 150 patients was followed during a 5-year period and those who developed PAD had higher mean CRP levels than those who did not develop PAD. Likewise, the association was seen with each increasing quartile of CRP level, with the highest quartile patients most likely to undergo future revascularization [2].

Although limited data exist, the severity of PAD may correlate with the serum level of CRP. Vainas et al [3] prospectively followed >300 patients with PAD and demonstrated a correlation of severity of disease stratified by ABI and serum CRP levels, that is, lower ABIs in patients with higher CRP values. Additionally, during a mean follow-up of 2 years, they demonstrated more progression of PAD in patients with higher tertiles of CRP values compared with lower serum levels [3]. Most importantly, cardiovascular morbidity and mortality were higher in patients with elevated high-sensitivity CRP (hs-CRP). These findings are in contrast to those from Musicant et al [4], who prospectively followed nearly 400 patients during a 3-year period. The primary endpoint was progression of disease quantified by either ABI, carotid duplex ultrasound, myocardial infarction, stroke, limb loss, or death. They were unable to note a difference between highest-tertile CRP and lowest-tertile levels [4].

3. Gender and CRP

During a 6-year period at a Life Line Screening Center, approximately 130,000 women and just over 70,000 men were screened for evidence of PAD, including data for conventional cardiovascular risk stratifications and the biochemical marker CRP [5]. In this specific report, women were more likely to have an ABI <0.9 (4.1% *v* 2.6%; $P < .001$) and have higher median CRP levels than men, 1.9 mg/L versus 1.4 mg/L, respectively ($P < .001$). Using this large database, there were statistically important interactions between the following classic risk factors: increasing age, coronary artery disease, diabetes mellitus, sex (women), CRP, and incidence of PAD defined by an ABI ≤0.9. Inflammatory mediators are perhaps different based on sex.

4. Inflammatory markers in PAD patients with intermittent claudication

Several investigators have analyzed the impact of biochemical markers in patients with PAD with regard to ambulation impairment. McDermott et al [6] published two articles during a 5-year period that assessed circulating biochemical markers and functional capacity. Initial work evaluated nearly 400 patients with ABI <0.9 and approximately half as many patients without peripheral vascular disease with the aim to assess four inflammatory markers (D-dimer, hs-CRP levels, fibrinogen, and serum amyloid A levels) and subsequent performance on lower-extremity functional testing. This testing was not standard treadmill testing, but 6-minute maximum walking distance, 4-m walk velocity at usual pace, and timed five chair rises from a chair without arm assistance.

When comparing the walking speed or distance in patients with or without peripheral vascular disease as defined by ABI, per quintile, the speed and distance were both inversely proportional to D-dimer levels and hs-CRP. Their data demonstrated a stepwise change in both markers on both methods of assessment of capacity, that is, distance and speed. For both of these preassessment markers (D-dimer and hs-CRP), participants with the lowest quintile values demonstrated 20% to 25% further walking, that is, a mean of 75 m/6 min or 12% to 18% faster velocity in 4-m speed when compared with those with the highest values.

The subsequent follow-up study by McDermott et al [7] sought to analyze newer biochemical markers, including homocysteine, interleukin 6, soluble intracellular adhesion molecules (sICAM-1 and SVCAM-1), as well as hs-CRP and D-dimer. This study added several more assessments, including a vertical accelerometer to assess activity units, during a 7-day period as outpatients and the addition of computed tomography of the calf before testing. The 4-m walking distance and 6-minute walk were performed, similar to first study.

This follow-up study included patients with documented PAD only. The 6-minute walk performance evaluation correlated with all six biochemical markers by statistical analysis using quartiles as reference. However, only four of the six biochemical markers were associated with slower 4-m walking speed; hs-CRP and homocysteine did not reach statistical significance.

The studies listed here by McDermott et al [6,7] have evaluated baseline biochemical markers before a modified exercise evaluation, but do not evaluate what happens to the biochemical markers over time. A study of 67 patients followed during a 3-month period with subsequent follow-up at a mean of 37 weeks was recently published in the *Journal of Cardiology* [8].

The authors reported maximal walking time increasing by 90%, but had declined to 64% at last follow-up, which was likely related to lack of continued walking. Endothelial function measured by flow-mediated dilatation also increased at the end of the program, and declined at last follow-up, but was still 30% above baseline values. With respect to hs-CRP concentration compared with baseline, a statistically significant decline was noted and an increase in ABI, despite no effect on the lipid panel at last follow-up.

This study focuses on short-term functional capacity and objective parameters associated with having a physician-directed program for exercise. Obviously, it would be remarkable to see compliance with such a vigorous program. However, with lack of funding and lack of motivation, this will continue to be a hurdle for most vascular specialists. Despite this issue, this small study provides hope that not only a functional benefit, but a biochemical effect as well, can be achieved when appropriate exercise programs are completed.

5. CRP and outcomes after endovascular interventions for PAD

Endovascular interventions for popliteal and infrapopliteal arteries (ie, tibial arteries) have shown excellent technical