Role of High Sensitivity C-Reactive protein In The Prediction of Future Cardiovascular Events in Patients Presenting With Acute Coronary Syndromes

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Abstract

Background and aims:

Inflammation appears to be pivotal in all phases of atherosclerosis from the fatty streak lesion to acute coronary syndromes. An important marker of inflammation is C-reactive protein .we thought to test the hypothesis that CRP measured at admission with acute coronary syndrome and at regular follow up durations is predictive of future cardiovascular events and to assess the relation of CRP levels to the complexity of coronary stenoses and to the coronary score as a surrogate of the total atherosclerotic burden.

Methods:

We prospectively recruited 91 patients presenting with acute coronary syndromes including those with ST elevation, clinical examination excludes those with evidence of infection or inflammation. All patients underwent coronary angiography (lesions were classified according to complexity into type A, B and C and coronary score was calculated by summing percent stenosis score times extent score over 15 coronary segments).Serum samples for measuring CRP level was withdrawn then patients was followed at 1, 4, 8 and 12 months and assessed for the occurrence of composite end points of nonfatal MI, UA or cardiac death. Samples for CRP were withdrawn in the 1st three follow up visits.

Results:

Admission CRP level could not predict future cardiovascular events (P=0.9) and did not correlate with complexity of coronary stenoses (P=0.42), meanwhile CRP at all follow up visits (1m,4m and 8m) correlated with both events (P=0.001,0.004and 0.01 respectively) and lesion complexity (P=0.001,0.01and<0.001respectively), CRP that preceded the event "pre-event CRP" was significantly higher than samples not followed by events. A cutoff value of 7.3 mg/l or 4.3 fold rise in CRP level had the highest sensitivity and specificity in detecting events. Despite being higher in patients developing events, coronary score did not correlate with any of the CRP samples.

Conclusions:

CRP done at admission is likely to be confounded by the inflammatory outburst that occur secondary to the occurrence of myocardial necrosis but it could be useful in following patients after acute coronary syndromes; its rise prior to the event may also indicate that CRP may not be a mere marker of plaque instability but also act as a mediator through its pro-inflammatory and pro-atherogenic effects. CRP is not a mere marker of the angiographic atherosclerotic burden but instead, a marker of coronary artery disease activity.

Key Words :

C-Reactive protein - Acute Coronary Syndromes - Cardiovascular Events

CONTENTS

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List of tables (page)

List of figures (page)

Introduction

Coronary artery disease is one of the leading causes of morbidity and mortality worldwide. Recent advances in basic sciences have established a fundamental role of inflammation in mediating all stages of atherosclerosis, i.e. initiation, growth & complications, all represent an inflammatory response to injury as it involves cytokines and other bioactive molecules and cells that are characteristic of inflammation e.g.(macrophages and T-lymphocytes).[(1)]

Acute coronary syndromes are responsible for almost all the morbidity and mortality of coronary artery disease, development of acute coronary syndromes occur with rupture of the fibrous cap overlying vulnerable atherosclerotic plaques with subsequent thrombosis leading to total or subtotal occlusion of a main epicardial coronary artery. The strength of the fibrous cap represents a balance between the extracellular matrix synthesis by smooth muscle cells -SMC's- and its degradation by proteolytic enzymes. The lipid core of atheromatous plaques contains 2 main types of inflammatory cells: T-lymphocytes which release interferon-γ (IF-γ) that inhibit SMC collagen production & macrophages which release collagen degrading matrix metalloproteinases and elastases, these enzymes promote matrix catabolism.[(1)]

Thus, in states of heightened intimal inflammation, the extracellular matrix that confers biomechanical strength of the plaque's fibrous cap is under double attack; decreased synthesis and increased degradation which results in weakening and thinning of the fibrous cap. Accordingly, inflammatory markers could be taken as a mean to assess the ongoing inflammatory process of atherosclerosis. [(1)]

CRP has been considered the analyte of choice after consideration of the various analytes stabilities, assay precision, accuracy, availability and the presence of standards for proper assay calibration.

Aim of the work

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The aim of this study is to:

1. Test the hypothesis that serial Hs-CRP measurements can predict recurrent future cardiovascular events (i.e. recurrent unstable angina, myocardial infarction or death) in patients presenting with acute coronary syndromes.

2. Assess the relation between Hs-CRP levels and the presence of complex angiographic coronary stenoses, which are known to represent high risk coronary plaques and also correlate the Hs-CRP to the total atherosclerotic burden.

3. Assess the role of different risk factor profiles in predicting the occurrence of future cardiovascular events in patients presenting with acute coronary syndromes.

Review of literature

Review of Literature

Inflammation and atherosclerosis

On initiation of an atherogenic diet rich in cholesterol and saturated fat, one of the first ultrastructural alterations is the accumulation of small lipoprotein particles in the arterial intima[(2)]. Lipoprotein particles bind to proteoglycan in the arterial intima and appear to exhibit increased susceptibility to oxidative and other chemical modifications including glycation and enzymatic processing by sphingomyelinase [(3, 4)] .LDL modification results in local cytokine elaboration, the cytokines then induce increased expression of adhesion molecules for leukocytes that cause their attachment and chemoattractant molecules that direct their migration into the intima. These chemoattractant molecules include 2 groups, monocyte chemoattractant protein 1(MCP1) and a group of T cell chemoattractant chemokines.

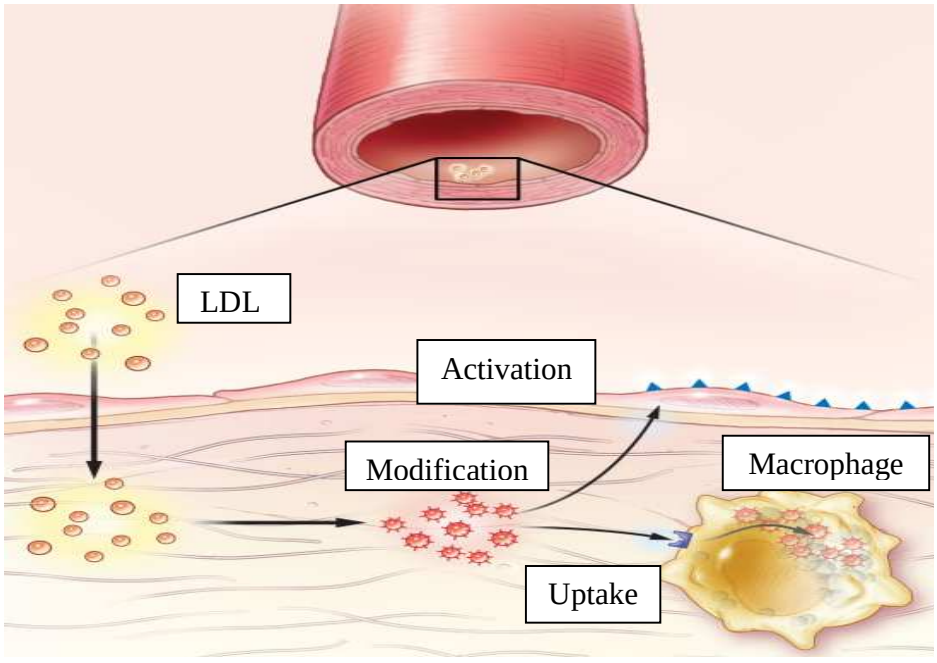

FIGURE 1: **Activating effect of LDL infiltration on inflammation in the artery**

"Inflammation, Atherosclerosis, and Coronary Artery Disease, NEJM, 352; 16 april 21, 2005."

The second morphologically definable event in the initiation of atheroma is leukocyte recruitment and accumulation. Very early after initiation of hypercholesterolemia, leukocytes and T lymphocytes adhere to the endothelium and diapedese between endothelial cell junctions to enter the intima.

The expression of certain leukocyte adhesion molecules on the surface of the endothelial cell regulates the adherence of monocytes and T cells to the endothelium [(5).] Two broad categories of leukocyte adhesion molecules exist, members of the immunoglobulin superfamily that include structures such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1(ICAM-1), both are expressed on the endothelial cell surface and bind both monocytes and lymphocytes. Adhesion molecules belonging to the immunoglobulin superfamily tend to promote tighter adhesive interactions and immobilization of leukocytes [(6).] Selectins constitute the other broad category of leukocyte adhesion molecules. The prototypical selectin, E-selectin (E for “endothelial,” the cell type that selectively expresses this particular family member), probably has little to do with early atherogenesis. E-selectin preferentially recruits polymorphonuclear leukocytes, a cell type seldom found in early atheroma, Other members of this family, including P-selectin (P for “platelet,” the original source of this adhesion molecule), may play a greater role in leukocyte recruitment in atheroma, Selectins tend to promote saltatory or rolling locomotion of leukocytes over the endothelium [(7,8).]

The monocyte, once recruited to the arterial intima, can there imbibe lipid and become a foam cell, or "lipid-laden macrophage", instead of the classical LDL receptor, various molecules known as “scavenger” receptors appear to mediate the excessive lipid uptake characteristic of foam cell formation, The longest studied of these receptors belong to the scavenger receptor-A family[(9,10).] These surface molecules bind modified rather than native lipoproteins and apparently participate in their internalization.

Other receptors that bind modified lipoprotein and may participate in foam cell formation include CD36 and macrosialin. Once macrophages have taken up residence in the intima and become foam cells, they frequently replicate. The factors that trigger macrophage cell division in the atherosclerotic plaque likely include macrophage colony-stimulating factor (M-CSF), interleukin-3 and granulocyte-macrophage colony-stimulating factor. [(9, 10)]

Thus far, the scenario of the evolving atheroma has invoked only such lipid-engorged leukocytes constituting what is known as the fatty streak. Withdrawal of the atherogenic diet or treatment with drugs that lower lipoprotein levels in plasma can reduce the extent of established lesions. Thus, fatty streaks composed primarily of macrophages are likely reversible, at least to some extent.

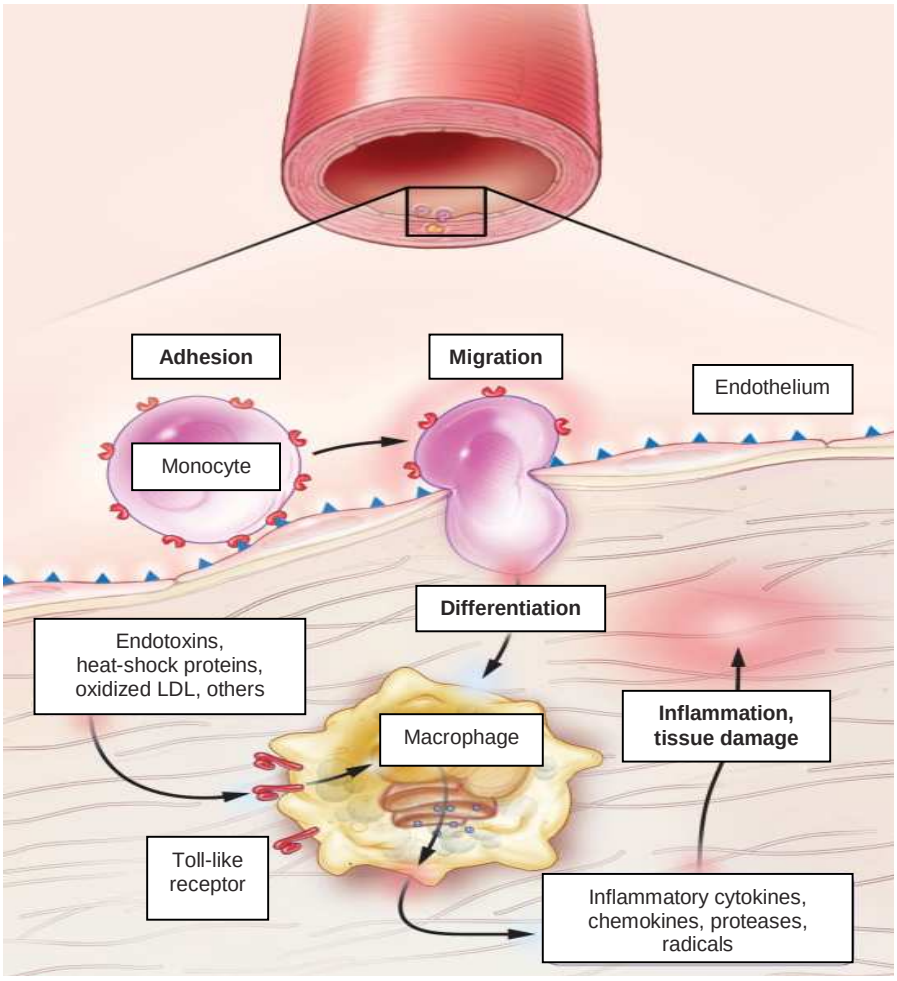

FIGURE 2: Inflammatory role of macrophage in atherosclerosis.

"Inflammation, Atherosclerosis, and Coronary Artery Disease, NEJM, 352; 16 april 21, 2005."

The subsequent evolution of atheroma into more complex plaques involves smooth muscle cells as well, The chemoattractants for smooth muscle cells likely include molecules such as platelet-derived growth factor (PDGF), a potent smooth muscle cell chemoattractant secreted by activated macrophages[(1).] Smooth muscle cells can then divide and elaborate extracellular matrix, promoting extracellular matrix accumulation in the growing atherosclerotic plaque. In this manner, the fatty streak can evolve into a fibrofatty lesion.