

Therapeutic Approaches for Reducing C-Reactive Protein (CRP) Levels and the Associated Cardiovascular Risk

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Abstract: Several inflammatory mediators regulate the evolution of atherosclerosis. C-reactive protein (CRP) is an acute-phase reactant, with a direct effect in inflammatory processes characterizing atherosclerosis. For this reason, CRP is actually considered as a factor, rather than simply a cardiovascular risk marker. The recent demonstration of CRP production not only by the liver, but also within atherosclerotic plaques by activated vascular cells, suggests a possible dual role, as both systemic and tissue molecule. Although more studies are needed, some therapeutic approaches to reduce CRP levels have been performed with encouraging results. Behavioral or pharmacologic interventions have been shown to reduce both CRP levels and the associated risk of cardiovascular acute events. Therefore, although most of national Cardiovascular Associations do not suggest high sensitivity CRP screening of the entire adult population as a public-health measure to stratify the cardiovascular risk, serum hs-CRP levels could be a promising target for therapies focused on reducing cardiovascular risk.

Keywords: Atherosclerosis, C-reactive protein, statins, cardiovascular risk.

INTRODUCTION

C-reactive protein (CRP) is an acute phase reactant secreted by the liver in response to inflammatory states [1]. During the last decade, the role of CRP in inflammatory diseases has been revised by showing new direct activities [2-5]. CRP is not produced only by the liver, but also in other tissues [6-10]. Furthermore, the ancient concept of CRP as inert marker of inflammation has been subverted by emerging evidences of direct pro-inflammatory activity [11-15]. Although the limitations due to the purity of compounds [15-19] and the very small number of animal models [20-25], CRP has been supported as a crucial factor in inflammatory diseases [26]. In particular, CRP appears to increase atherosclerosis at very low concentrations (values between 3 and 10 $\mu\text{g/mL}$). CRP has also been shown to predict dangerous atherosclerotic complications, such as myocardial infarction, stroke and peripheral artery disease [27]. A positive correlation has been also shown between CRP serum levels and with coronary atherothrombosis [28]. On the basis of these evidences and due to the high cost of high sensitivity (hs)-CRP dosage, the American Heart Association and Centers for Disease Control and Prevention recommended to use CRP in cardiovascular risk assessment only in subjects with an intermediate Framingham risk score (10-20 %) [29]. Limitations in the clinical use of CRP are mainly due to the low specificity of this factor. In fact, CRP has been found elevated in several diseases [30-32]. Intriguingly, inflammatory diseases with chronic high levels of CRP have been shown associated with the increase of atherosclerosis. Although highly speculative, this element further suggests that CRP should be considered one of the most important

pro-atherosclerotic mediators. Clinical trials based on therapeutic strategies lowering CRP levels are needed to answer to the ancient question: "Is CRP a pro-atherosclerotic factor or only an innocent marker?" [33].

CRP LOWERING THERAPEUTIC STRATEGIES IN ATHEROSCLEROSIS

The CRP plasma level cut off in healthy population is about 2 $\mu\text{g/mL}$ [34]. Less than this value, CRP is considered normal [35]. CRP levels are increased very rapidly few hours after acute events, such as surgery and infections [36, 37]. The increased plasma levels of CRP are quite different depending on acute inflammatory processes, such as bacterial infections [37], and in chronic inflammatory diseases, such as atherosclerosis [38]. Subjects with acute infections display a 10-fold increase of levels of CRP in comparison with atherosclerotic patients [37, 38]. Liver production and release of CRP into the circulation is the main player in increasing its plasma concentrations [39, 40]. Once released, CRP remains in the circulation for about 19 hours [33]. CRP half-life time and development of acute events have to be considered a crucial interference for studies investigating CRP lowering therapies. In following we will review some of different approaches for reducing CRP.

DIET AND BEHAVIOURAL INTERVENTIONS

CRP levels have been correlated to the degree and the distribution of adiposity [41-44]. Furthermore, weight loss due to caloric restriction has been shown to reduce CRP levels in obese subjects [45, 46]. These evidences strongly support life style as a key determinant in CRP-mediated cardiovascular risk. Regular physical activity, smoking cessation and light alcohol intake have been shown to lower CRP levels in several studies [47-55]. Dietary factors also modulated CRP levels [56]. At present, ω -3 polyunsaturated fatty acids are under investigation to understand the mechanisms by which fish consumption reduces coronary artery disease [57, 58]. A possible direct anti-inflammatory activity induced by

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ω -3 polyunsaturated fatty acid intake has been suggested [59]. However, the modification of CRP level induced by ω -3 polyunsaturated fatty acid supplementation is still controversial [60-62]. Low-fat, low cholesterol or low glycaemic diets seem to play a role in lowering CRP levels [60, 63-65]. Blood concentrations of vitamins with anti-oxidant activity have also been associated with the decrease of CRP levels [66]. However, failure of reducing cardiovascular risk in large clinical trials with vitamin supplementation has strongly reduced the importance of these first observations [67]. Recently, studies have shown that vitamin E and vitamin C supplementation reduced the increase of CRP levels after meal [68]. Significant results have also been obtained in hyperhomocysteinemia and type 2 diabetes patients, in which multivitamin supplement and vitamin E at high doses significantly lowered hs-CRP levels [69, 70]. Further studies are needed to clarify the role of vitamin supplementation as a therapeutic strategy to reduce CRP levels.

PHARMACOLOGIC INTERVENTIONS

Aspirin (an anti-platelet and anti-inflammatory drug) reduces the risk of future cardiovascular events [71, 72]. If aspirin may also decrease CRP levels is still a topic for debate. High doses of aspirin or low doses in combination with clopidogrel lowered CRP levels [73-75]. Low doses (between 81 and 100 mg/day) of aspirin alone failed to decrease CRP levels [76-78]. This suggests that anti-inflammatory rather than anti-platelet doses of aspirin may influence CRP production. Treatment with other anti-inflammatory drugs, such as cyclooxygenase-2 (COX-2) inhibitors, may support that anti-inflammatory therapies lower CRP levels [79, 80]. Further studies are needed to clarify this issue, also considering the adverse effects of these medications in cardiovascular diseases.

Anti-diabetic agents also reduce CRP levels [81, 82]. Given the exception of insulin, thiazolidinedione derivatives reduced CRP serum concentrations in humans [83]. Although very promising as CRP-lowering agents, these studies are in contrast with more recent publications showing that some thiazolidinediones, such as rosiglitazone, increase the incidence of acute cardiovascular events [84, 85].

Estrogens and anti-estrogens therapies have been studied with different results. Oral estrogen replacement therapy increased CRP levels [86, 87], while transdermal therapy did not modify CRP production [87-89]. Anti-estrogen therapy has been found to significantly decrease CRP plasma levels [90]. These data suggest that estrogens are inducers of CRP secretion, but further investigations are needed to understand these biological pathways. Several studies showed that beta-blockers, calcium-antagonists and inhibitors of renin-angiotensin system reduce CRP levels in both acute and chronic manifestations of atherosclerosis [91-96]. However, other studies with these agents (enalapril, candesartan and amlodipine) did not confirm these data [95, 97-99]. Diuretics, such as hydrochlorothiazide, reduced CRP plasma levels only in combination with valsartan (an angiotensin II receptor antagonist) [100-102]. These data indicate that beta-blockers, calcium-antagonists and inhibitors of renin-angiotensin system rather than diuretics may lower CRP levels in humans. Lipid-lowering agents are pharmacologic molecules, which are capable of reducing both CRP levels and CRP-induced pro-inflammatory activities. Our research group has recently shown that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduce CRP concentrations through a direct mechanism on hepatocytes, independently on lowering cholesterol [103]. Statins also inhibit CRP-mediated pro-inflammatory activity on human leukocytes [104]. *In vivo* studies confirmed that statins re-

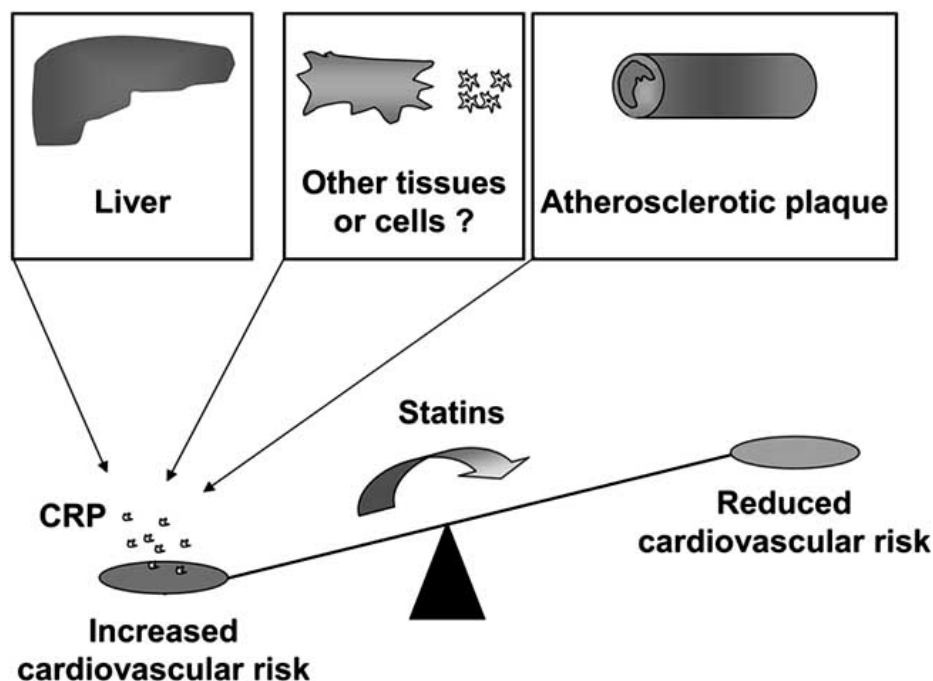


Fig. (1). CRP is a cardiovascular risk factor. CRP is a soluble mediator mainly secreted by liver. Other tissues, such as atherosclerotic plaques, rheumatoid synovium, kidney, neurons, lung, also produce little quantities of CRP. Given the important role of CRP as an active factor in the increase of cardiovascular risk, the pharmacologic inhibition of CRP production and activity may represent a crucial step for reducing atherosclerosis. At present, statins are the most promising agent, which reduces CRP-mediated cardiovascular risk.

duce CRP plasma levels after a treatment of few weeks and independently on cholesterol levels [105, 106]. In 2007, JUPITER (Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin) has been designed to determine if treating patients with no evidence of pre-existing cardiovascular disease and low to normal LDL-C but elevated CRP would reduce major cardiovascular events with 20mg rosuvastatin once daily [107]. This study has been stopped at the end of March 2008, because there was unequivocal evidence of a reduction in cardiovascular morbidity and mortality amongst patients who received rosuvastatin when compared to placebo. This trial represents the first contribution on the effect of statins in primary prevention. A direct effect on lowering CRP has been also shown after a treatment with fenofibrate [108, 109]. Other lipid lowering agents, such as ezetimibe and niacin have been shown to reduce CRP in combination with statins [110, 111].

CONCLUSIONS

In the present review, we focused our attention on CRP pro-inflammatory activities and the associated increase in cardiovascular risk. Reduction of CRP plasma levels may represent a new approach for reducing inflammatory state during atherosclerogenesis. Emerging evidence suggests that among several agents, statins are the more promising molecules to reduce both CRP levels and CRP-mediated pro-inflammatory activities (Fig. 1). Data from Jupiter Trial will probably support the use of statins for reducing CRP-induced cardiovascular risk. We are waiting for the publication of Jupiter Trial results to understand these new findings.

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