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## **C-reactive protein: a marker or a player?**

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## Abstract

It has been suggested that type 2 diabetes may in part be precipitated or accelerated by an acute phase reaction as part of the innate immune response, in which large amounts of cytokines are released from adipose tissue, creating a low-grade inflammatory milieu. Also, there is solid evidence that atherosclerosis is an immune-mediated inflammatory disease. Therefore, it is reasonable to imply low-grade inflammation as an important pathogenetic factor in terms of atherosclerosis and cardiovascular events in type 2 diabetes patients. Over the past years, there have been a lot of promising clinical markers proposed to link inflammation and atherosclerosis. Of these markers, high sensitive C-reactive protein (hsCRP) might be a prognostic marker for further cardiovascular events, although recently refuted. In this issue of *Clinical Science*, Castoldi et al demonstrate that in type 2 diabetic patients, categorized in low (<1.0 mg/L), medium (1.0-3.0 mg/L) and high (>3 mg/L), serum levels of hsCRP correlate with LPS-stimulated release of IL-1 $\beta$  and IL-6 in whole blood. This finding may indicate that low-grade inflammatory activity might influence cytokine production in these patients.

There is solid evidence that atherosclerosis is an immune-mediated inflammatory disease [1]. The nature of the atherosclerotic process can be described as an ongoing inflammatory process where fatty streaks, formed by oxidative lipoproteins, are one of the earliest changes seen. This state is accompanied by monocytes and T lymphocytes drawn to the vascular endothelium by cytokines, chemokines, migrating and colony-stimulating factors, maintaining an inflammatory milieu. Once adherent to the endothelium, monocytes transmigrate into the tunica intima, the innermost layer of the arterial wall, are transformed to macrophages and begin to express scavenger receptors and give rise to foam cells. Macrophages play an important role, not only as lipid scavenger cells, but also as immunocompetent cells secreting pro-inflammatory cytokines, *e.g.* tumour necrosis factor alpha (TNF- $\alpha$ ) and different interleukins (IL), such as IL-1 $\beta$ , IL-8 and IL-10. Several discernable factors have been proposed to exacerbate and accentuate the above proinflammatory in the arteries, such as cigarette smoking, dyslipidemia, hypertension, hereditary factors, infectious microorganisms and diabetes.

Over the past years, there have been a lot of promising clinical markers proposed to link inflammation and atherosclerosis [2]. Measuring inflammatory markers in serum may provide clinicians with additional information regarding a patient's risk for cardiovascular disease (CVD). Of these markers, C-reactive protein (CRP), TNF- $\alpha$  and IL-6 have been most widely studied. Although simple measurements of white blood cell count and its relationship to CVD have been reported [3], the most promising is CRP as a putative prognostic and predictive marker for cardiovascular events. CRP release from the liver is promoted by IL-1 $\beta$ , IL-6 and TNF- $\alpha$  as an acute phase reactant in response to inflammation. In an acute bacterial infection, *e.g.* pneumococcal pneumonia, the levels of serum CRP usually amount to several hundreds mg/L. In contrast, the cut points of low-, average- and high risk for CVD corresponds to approximate tertiles of values <1.0, 1.0-3.0 and >3.0 mg/L,

respectively, based on population studies [4]. It has been suggested that a cut-off limit level > 3 mg/L indicates low-grade inflammation, which in turn might be a prognostic marker for further cardiovascular events [5], although recently refuted [6].

In a series of elegant experiments from Verma's group, it was proposed that CRP is not only a marker for, but a player in, CVD. CRP may directly promote atherosclerosis and endothelial inflammation by attenuating release of nitric oxide (NO), a key molecule in the endothelium that plays a pivotal role in the maintenance of the vascular tone [7]. In addition, besides the potent vasodilator effects of NO, it mediates many protective functions in the endothelium, *e.g.* inhibits expression of pro-inflammatory cytokines, chemokines and leukocyte adhesion molecules, thereby limiting vascular recruitment of leukocytes and platelets [8]. NO also inhibits vascular smooth muscle cell proliferation, an early sign of atherosclerosis. Therefore, CRP may have an important deleterious role in the atherosclerotic process, *i.e.* by inhibiting NO formation. However, the involvement of CRP as a functional player in the endothelium has recently been questioned, as it was suggested that the proinflammatory effects by CRP might be due to a contaminating artefact in the commercial CRP preparation [9]. Recently, the same authors demonstrated that injection of contaminate-free human CRP in rats increases myocardial infarct size through a complement mechanism. An effect that was blunted after administration of a specific CRP inhibitor, which could be harnessed to advantage in the treatment of CVD [10].

In this issue of *Clinical Science*, Castoldi et al [11] demonstrate that in type 2 diabetic patients categorized with low (<1.0 mg/L), medium (1.0-3.0 mg/L) and high (>3 mg/L) serum levels of hsCRP there is a correlation between hsCRP and LPS-stimulated release of IL-1 $\beta$  and IL-6 in whole blood. This finding may indicate that low-grade inflammatory activity might influence cytokine production in these patients. In fact, population studies show strong correlation between proinflammatory biomarkers, such as

CRP, IL-6, and TNF- $\alpha$ , and perturbations in glucose homeostasis, obesity, and atherosclerosis [12]. Interestingly, CRP levels might be independently related to the degree of insulin resistance. In a *post-hoc* analysis of the predictive value of CRP for the risk of developing diabetes in the WOSCOPS cohort of middle aged men, a dose-dependent correlation, independent of established risk factors, was indeed found [13]. The acute-phase responses associated with type 2 diabetes thus offer insights into plausible mechanisms by which atherosclerosis is accelerated in type 2 diabetes, including mediation by acute-phase proteins themselves [12].

It has been suggested that type 2 diabetes may in part be precipitated or accelerated by an acute phase reaction as part of the innate immune response, in which cytokines are released from adipose tissue, creating an inflammatory milieu [14]. Low-grade inflammation might be an important pathogenetic factor in the development of insulin resistance and type 2 diabetes. In general, visceral obesity leads to insulin resistance and endothelial dysfunction mainly through a cascade of pro-inflammatory agents being released from the visceral adipocytes. According to this hypothesis, cytokines exert toxic effects on endothelial cells and cause increased capillary permeability. Cytokines produced locally in inflamed plaques, which are common in poorly controlled diabetes, could impose oxidative stress and endothelial dysfunction that might further aggravate the atherosclerotic process. Furthermore, insulin resistance leads to hyperglycaemia that also promotes an inflammatory milieu. Moreover, hypertension and dyslipidemia, usually seen in overweight type 2 diabetes patients, might contribute to the low-grade inflammation. In fact, multifactorial drug treatment in patients with type 2 diabetes reduces the risk for cardiovascular events [15], suggesting that these factors are interrelated, numerous and complex. More specific and sensitive biomarkers should be identified, which may predict

early disturbances in insulin sensitivity and endothelial function and link type 2 diabetes to atherosclerosis. Also, inflammatory signalling pathways need to be explored in greater detail.

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