Low-grade chronic inflammation has been proposed to play a central role in atherosclerosis\(^1,2\), as well as in other types of vascular damage, and measuring the level of inflammatory markers in the blood can provide prognostic information regarding cardiovascular disease (CVD) risk\(^1,2\). A serum level of C-reactive protein (CRP), determined with a high-sensitivity assay, is at the moment the best studied inflammatory marker, and CRP has been used to enhance risk prediction based on Framingham risk score and Reynolds risk score in apparently healthy women and men\(^1,2,3\).

In this issue of *The Journal*, Provan and colleagues\(^4\) report interesting data regarding the putative role of low-grade chronic inflammation in CVD with special reference to the well established increased CVD risk seen in patients with rheumatoid arthritis (RA)\(^5\). Provan and colleagues\(^4\) studied a cohort of a little more than 100 patients with RA, and they found that serum levels of CRP above the median (\(> 3.80 \text{ mg/l}\)) at baseline were associated with increased central artery stiffness at followup 15 years later. As increased central or large artery stiffness is a well established marker of increased CVD risk\(^6\), Provan and colleagues\(^4\) speculate that poor control of RA, as reflected by higher levels of CRP, and thereby accompanying inflammatory damage to the elastic arteries, may explain the increased CVD risk seen in patients with RA. As a consequence, they discuss that early active disease management by use of disease modifying antirheumatic drugs to control inflammation may help to reduce the risk of later CVD in patients with RA. However, although it certainly would be desirable if tight control of the inflammatory processes caused by RA would eventually lead to a decreased risk of CVD in RA patients\(^5\), things may be somehow more complicated than initially thought. Thus, higher serum CRP levels in RA patients may be caused by other factors than the inflammatory rheumatic disease\(^7,8\), and further, studies using Mendelian randomization have shown that genetically elevated levels of CRP are associated neither with increased CVD risk\(^9\) nor with measures of aortic stiffness\(^10\), suggesting that the inflammatory biomarker used by Provan and colleagues\(^4\) is merely a risk marker rather than a causal factor in the disease processes that eventually lead to clinical CVD, in patients with and without RA for that matter.

Before discussing the above issues in more detail, it is worthwhile to briefly consider the concept of low-grade inflammation\(^1,2,3,11\). Normal human serum contains CRP concentrations less than \(10 \text{ mg/l}\), and it is generally accepted that mild inflammation and viral infections cause elevation of CRP in the \(10–40 \text{ mg/l}\) range, while active inflammation and bacterial infections produce levels of \(40–200 \text{ mg/l}\)\(^12\). With the development of high-sensitivity CRP assays capable of measuring the very low CRP levels normally found in human serum (\(0.1–2.5 \text{ mg/l}\)), it was possible to show that apparently healthy individuals, who had serum CRP levels between \(~2\) and \(10 \text{ mg/l}\), had a substantially increased risk of CVD, independently of all well established traditional CVD risk factors\(^1,2,3\). As the increased CVD risk could be identified within the serum CRP range otherwise considered to be normal, the concept of a low-grade inflammatory state evolved\(^1,2,3,11\). In this context, it is worth repeating that the median serum CRP level of the RA patient population studied by Provan and colleagues\(^4\) was \(3.80 \text{ mg/l}\), i.e., within the low-grade inflammation range and not in the high-grade inflammation range\(^11\).

Thus, after this brief comment on the concept of low-grade inflammation\(^1,2,3,11\), it is time to discuss putative causes of the persistent low-grade inflammation that may be found in some apparently healthy women and men\(^1,2,3\), including patients with well controlled RA or mild disease activity\(^13\). Initially, it was thought that this low-grade inflammatory state was mainly the result of minor chronic insults such as smoking, chronic bronchitis, chronic gingivitis, and persistent bacterial infections with microorganisms such as *Helicobacter pylori* and *Chlamydia pneumoniae*\(^1,2,14\).
but from the mid-1990s it became clear that higher serum levels of CRP were also closely associated with overweight and many of the metabolic factors closely associated with the overweight condition\textsuperscript{13,15}. Thus, although increasing age, smoking, symptoms of chronic bronchitis, \textit{H. pylori} and \textit{C. pneumoniae} infections, all associate with raised serum concentrations of CRP within the low-grade inflammation range\textsuperscript{14,15}, the relationships between serum CRP levels and metabolic variables, such as body mass index, waist circumference, plasma glucose, prevalence of type 2 diabetes, blood pressure, prevalence of hypertension, plasma triglyceride, serum insulin levels, and estimates of insulin resistance have been found to be as strong as the relationships between serum CRP levels and the aforementioned factors\textsuperscript{14,15}. Further, it is noteworthy that higher serum levels of CRP in addition to CVD predict new-onset hypertension and new-onset type 2 diabetes\textsuperscript{1}. As a likely mechanistic link between overweight and increased synthesis of CRP by the liver, it has been shown that human subcutaneous adipose tissue secretes interleukin 6 (IL-6) \textit{in vivo}\textsuperscript{16}, and it has been estimated that \textasciitilde30\% of the total circulating concentrations of IL-6 originate for adipose tissue in healthy subjects\textsuperscript{16}. So, adipose tissue is indeed an active proinflammatory organ. In this context, in discussing “metabolic inflammation” versus inflammation caused by inflammatory diseases, it is noteworthy that human subcutaneous adipose does not secrete tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\))\textsuperscript{16}. With respect to lifestyle habits other than smoking, which, as mentioned above, are associated with increased serum concentrations of CRP\textsuperscript{8,14}, it is important to note, regarding RA patients and low-grade inflammation, that higher serum CRP levels are negatively correlated with level of physical activity\textsuperscript{8}, as significantly lower physical activity levels were reported among women with RA in the Nurses Health Study\textsuperscript{17}.

Therefore, is it possible that metabolic factors and lifestyle risk factors discussed above, rather than the rheumatic disease itself, could explain the low-grade inflammation state found in Provan and colleagues’ RA patients at baseline in 1992, or at least partly explain the condition? The answer to this question is simple: we do not know. Thus, Provan and colleagues\textsuperscript{4} do not provide the readers of The Journal with any baseline information about their RA patient cohort related to prevalence of metabolic risk factors and lifestyle risk factors. In particular, missing baseline information about estimates of overweight and body composition, level of physical activity, smoking habits, blood pressure levels, serum insulin levels, and estimates of insulin resistance, all factors reported in various studies to be relatively closely correlated with both serum CRP levels and large artery stiffness\textsuperscript{8,18,19}, makes the results reported by Provan and colleagues difficult to interpret in depth discussing presence of low-grade inflammation in patients with RA. The relevance of this point is further highlighted by a recent report in The Journal by Crowson and colleagues\textsuperscript{20}, that patients with RA were found to have significantly increased waist circumference and elevated blood pressure status compared with controls, and although the results in the medical literature are not entirely consistent, several articles have been published describing that patients with RA have a higher prevalence of metabolic disturbances, in particular hypertension and insulin resistance\textsuperscript{21}. In this context, it is interesting that Chung and colleagues\textsuperscript{7} found that RA patients with insulin resistance had significantly higher serum CRP levels compared with insulin-sensitive RA patients [median (interquartile range): 6 mg/l (3–14) vs 3 mg/l (3–9); \(p = 0.01\)]. Further, it is of note that in a study by Rosenvinge and colleagues\textsuperscript{21} RA patients with active disease showed marked insulin resistance compared with well matched controls, but the level of insulin resistance was not influenced by anti-TNF-\(\alpha\) therapy despite marked reductions in serum levels of CRP, which changed from the high-grade to the low-grade inflammation range. Thus taken together, it is likely that “metabolic inflammation” also contributes to raised serum CRP levels in the low-grade inflammation range in RA patients with well controlled or mild disease activity.

As mentioned above, studies using Mendelian randomization have shown that genetically elevated serum levels of CRP are associated neither with increased CVD risk\textsuperscript{9} nor with measures of aortic stiffness\textsuperscript{10}, suggesting that CRP is merely a risk marker rather than a causal factor in the disease processes that eventually lead to clinical CVD. Thus, when discussing “metabolic inflammation” versus inflammation caused by rheumatic diseases, it would have been interesting if Provan and colleagues\textsuperscript{4} had measured inflammatory cytokines in the blood, such as IL-6 and TNF-\(\alpha\), and had shown that baseline levels of these inflammatory cytokines were also associated with increased central artery stiffness at followup 15 years later.

So, what is the lesson to be learned from the article by Provan and colleagues\textsuperscript{4} and the present article: elevated serum CRP levels above > 3.80 mg/l are associated prospectively with increased large artery stiffness, an established risk factor for CVD\textsuperscript{2}; physicians caring for patients with RA should consider the presence of metabolic CVD risk factors, possibly requiring pharmacological or nonpharmacological treatment, as well as uncontrolled rheumatic disease in RA patients with raised serum CRP levels within the low-grade inflammation range, a view supported by experts in the field\textsuperscript{5}.

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Correction

Low-grade Chronic Inflammation and Vascular Damage in Patients with Rheumatoid Arthritis: Don’t Forget “Metabolic Inflammation”

doi:10.3899/jrheum.110006C1