Low-grade Chronic Inflammation and Vascular Damage in Patients with Rheumatoid Arthritis: Don't Forget "Metabolic Inflammation"

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 colleagues⁴ 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 colleagues⁴ 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 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 risk⁶, Provan and colleagues⁴ 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 patients⁵, 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 risk⁹ nor with measures of aortic stiffness¹⁰, suggesting that the inflammatory biomarker used by Provan and colleagues⁴ 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 mg/l, and it is generally accepted that mild inflammation and viral infections cause elevation of CRP in the 10–40 mg/l range, while active inflammation and bacterial infections produce levels of 40–200 mg/l¹². 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 mg/l), it was possible to show that apparently healthy individuals, who had serum CRP levels between ~ 2 and 10 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 colleagues⁴ was 3.80 mg/l, i.e., within the low-grade inflammation range and not in the high-grade inflammation range¹¹.

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 activity¹³. 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},

See Early prediction of increased arterial stiffness in RA patients with chronic inflammation,
page 606

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^{14,15}. Thus, although increasing age, smoking, symptoms of chronic bronchitis, *H. pylori* and *C. pneumoniae* infections, all associate with raised serum concentrations of CRP within the low-grade inflammation range^{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^{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 diabetes¹. 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) *in vivo*¹⁶, and it has been estimated that ~30% of the total circulating concentrations of IL-6 originate for adipose tissue in healthy subjects¹⁶. 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- α (TNF- α)¹⁶. With respect to lifestyle habits other than smoking, which, as mentioned above, are associated with increased serum concentrations of CRP^{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 activity⁸, as significantly lower physical activity levels were reported among women with RA in the Nurses Health Study¹⁷.

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 colleagues⁴ 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^{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 colleagues²⁰,

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 resistance⁷. In this context, it is interesting that Chung and colleagues⁷ 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 colleagues²¹ 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- α 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 risk⁹ nor with measures of aortic stiffness¹⁰, 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 colleagues⁴ had measured inflammatory cytokines in the blood, such as IL-6 and TNF- α , 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 colleagues⁴ 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 CVD⁶; 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 field⁵.

JØRGEN JEPPESEN, MD, DMSci,
Associate Professor,
Department of Medicine,
Division of Cardiology,
Copenhagen University Hospital Glostrup,
Ndr. Ringvej, DK-2600 Glostrup, Denmark;
and Faculty of Health Sciences,
University of Copenhagen,
Copenhagen, Denmark

REFERENCES

1. Ridker PM, Silvertown JD. Inflammation, c-reactive protein, and atherothrombosis. *J Periodontol* 2008;79 Suppl:1544-51.
2. Libby P, Ridker PM, Hansson GK; Leducq Transatlantic Network on Atherothrombosis. Inflammation in atherosclerosis: from pathophysiology to practice. *J Am Coll Cardiol* 2009;54:2129-38.
3. Ridker PM, Cook N. Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham Risk Scores. *Circulation* 2004;109:1955-9.
4. Provan SA, Angel K, Semb AG, Mowinkel P, Agewall S, Atar D, et al. Early prediction of increased arterial stiffness in patients with chronic inflammation: a 15-year follow-up study of 108 patients with rheumatoid arthritis. *J Rheumatol* 2011;38:606-12.
5. Pieringer H, Pichler M. Cardiovascular morbidity and mortality in patients with rheumatoid arthritis: vascular alterations and possible clinical implications. *Q J Med* 2011;104:13-26.
6. Willum-Hansen T, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, et al. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation* 2006;113:664-70.
7. Chung CP, Oeser A, Solus JF, Avalos I, Gebretsadik T, Shintani A, et al. Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. *Atherosclerosis* 2008;196:756-63.
8. Jeppesen J, Hansen TW, Olsen MH, Rasmussen S, Ibsen H, Torp-Pedersen C, et al. C-reactive protein, insulin resistance and risk of cardiovascular disease: a population-based study. *Eur J Cardiovasc Prev Rehabil* 2008;15:594-8.
9. Zacho J, Tybjaerg-Hansen A, Jensen JS, Grande P, Sillesen H, Nordestgaard BG. Genetically elevated C-reactive protein and ischemic vascular disease. *N Engl J Med* 2008;359:1897-908.
10. Schumacher W, Cockcroft J, Timpson NJ, McEniery CM, Gallacher J, Rumley A, et al. Association between C-reactive protein genotype, circulating levels, and aortic pulse wave velocity. *Hypertension* 2009;53:150-7.
11. Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation* 2003;108:2957-63.
12. Clyne B, Olshaker JS. The C-reactive protein. *J Emerg Med* 1999;17:1019-25.
13. Graf J, Scherzer R, Grunfeld C, Imboden J. Levels of C-reactive protein associated with high and very high cardiovascular risk are prevalent in patients with rheumatoid arthritis. *PLoS One* 2009;4:e6242.
14. Mendall MA, Patel P, Ballam L, Strachan D, Northfield TC. C reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. *BMJ* 1996;311:1061-5.
15. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol* 1999;19:972-8.
16. Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor- α , in vivo. *J Clin Endocrinol Metab* 1997;82:4196-200.
17. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation* 2003;107:1303-7.
18. McEniery CM, Yasmin, Maki-Petaja KM, McDonnell BJ, Munnelly M, Hickson SS, et al; Anglo-Cardiff Collaboration Trial Investigators. The impact of cardiovascular risk factors on aortic stiffness and wave reflections depends on age: the Anglo-Cardiff Collaborative Trial (ACCT III). *Hypertension* 2010;56:591-7.
19. Hansen TW, Jeppesen J, Rasmussen S, Ibsen H, Torp-Pedersen C. Relation between insulin and aortic stiffness: a population-based study. *J Hum Hypertens* 2004;18:1-7.
20. Chung CP, Oeser A, Solus JF, Avalos I, Gebretsadik T, Shintani A, et al. Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. *Atherosclerosis* 2008;196:756-63.
21. Rosenvinge A, Krogh-Madsen R, Baslund B, Pedersen BK. Insulin resistance in patients with rheumatoid arthritis: effect of anti-TNF- α therapy. *Scand J Rheumatol* 2007;36:91-6.

J Rheumatol 2011;38:595-7; doi:10.3899/jrheum.110006

Correction

Low-grade Chronic Inflammation and Vascular Damage in Patients with Rheumatoid Arthritis: Don't Forget "Metabolic Inflammation"

Jeppesen J. Low-grade chronic inflammation and vascular damage in patients with rheumatoid arthritis: Don't forget "metabolic inflammation". *J Rheumatol* 2011;38:595-7. Reference 20 of this editorial should read as follows. Crowson CS, Myasoedova E, Davis JM 3rd, Matteson EL, Roger VL, Therneau TM, et al. Increased prevalence of metabolic syndrome associated with rheumatoid arthritis in patients without clinical cardiovascular disease. *J Rheumatol* 2011;38:29-35. We regret the error.
doi:10.3899/jrheum.110006C1