C-reactive protein in healthy and in sick populations

See page 1598 for the article to which this Editorial refers

C-reactive protein, named in 1930, is the classic ‘acute phase reactant’, the plasma values of which can increase 10 000-fold in response to tissue injury and infection\[^1\]. In recent years, it has been studied as a potential marker of more subtle and persistent systemic alterations that may be loosely called ‘low-grade inflammation’\[^2\]. If the sharp increases that occur during acute-phase responses are ignored, then long-term plasma C-reactive protein values show about the same degree of year-to-year consistency within individuals as do some of the more extensively studied risk factors such as blood cholesterol and blood pressure\[^3\]. Moreover, highly sensitive assays for C-reactive protein are now available that can precisely measure values within the range less than 10 mg.l\(^{-1}\) and thereby detect low-grade inflammation that would previously not have been noticed\[^1\].

Since 1996, 11 long-term prospective studies have reported on the possible relevance of C-reactive protein to coronary heart disease in the general population\[^4\]. In aggregate, these community-based studies involved 1949 cases of non-fatal myocardial infarction or death from coronary heart disease following a mean weighted follow-up of 9 years after baseline blood collection. All but one study adjusted for age, sex, smoking and some classical vascular risk factors, and there was no significant heterogeneity among their separate results ($\chi^2_{10} = 5.7; P > 0.1$). A combined analysis of them gives a risk ratio for coronary heart disease of 2.0 (95% confidence interval [CI], 1.6–2.5). This risk ratio is based on a comparison of people with baseline C-reactive protein values in the top third compared with those in the bottom third of the population, corresponding to mean usual C-reactive protein values of 2.4 vs 1.0 mg.l\(^{-1}\)\[^2\].

Although the strength of this association with coronary heart disease risk is comparable with that for other better studied risk factors such as plasma fibrinogen, the causal relevance of C-reactive protein to coronary heart disease remains uncertain. Plasma C-reactive protein might be a direct mediator of vascular damage. This possibility is suggested by its frequent detection in atherosclerotic plaques and by several possible mechanisms that have been proposed to account for any vascular effects, although none is, as yet, proved\[^9\]. It might, however, be that plasma C-reactive protein is mainly a marker of known or suspected vascular risk factors such as smoking and obesity\[^6\]; a marker of chronic infective processes possibly correlated with coronary heart disease risk such as persistent infection with Chlamydia pneumoniae\[^7\]; or a marker of the extent of subclinical disease (since atherosclerosis is partly an inflammatory lesion\[^8\]). In these cases, C-reactive protein itself would not be of causal relevance to coronary heart disease.

Despite the uncertainties about the relevance of C-reactive protein to coronary heart disease in the general population, a number of studies have investigated C-reactive protein in other settings, including long-term studies of populations defined on the basis of pre-existing conditions such as vascular disease\[^9\], diabetes\[^10\] and chronic renal disease\[^11\]. Compared with studies in the general population, interpretation of studies in these ‘sick’ populations is complicated by an increased likelihood that factors related to pre-existing disease itself may alter both C-reactive protein values and coronary heart disease risk. Such distortions might be particularly likely in patients with pre-existing coronary heart disease. This is because C-reactive protein values can be influenced not only by the severity of disease itself but also by the effects of medications prescribed for coronary heart disease (for example, certain ‘statin’ drugs may lower plasma C-reactive protein values\[^8\]) and of changes in habits and risk factors following a diagnosis of coronary heart disease (for example, smoking cessation and weight reduction). Even if studies in sick populations attempt adjustments for such potentially distorting factors, the results may still be of uncertain validity. Residual biases are possible both because baseline values of some confounders may be inaccurate measurements of their long-term ‘usual’ values, thereby resulting in inadequate statistical adjustments\[^12\]; and because some possible confounders may not be measured at all.

The study of Garcia-Moll et al\[^13\] in this issue illustrates the challenges of investigating C-reactive protein in sick populations. They made C-reactive protein measurements in 911 British patients with chronic stable angina subsequently monitored for a median duration of about 18 months. The authors correctly point out that the 29 myocardial infarctions and deaths from coronary heart disease recorded in their study were too few for reliable analyses of the predictive ability of C-reactive protein. By comparison, three previously published long-term prospective studies of C-reactive protein in cohorts defined on the
basis of pre-existing coronary heart disease have involved a total of 604 cases of non-fatal myocardial infarction or death from coronary heart disease following a mean weighted follow-up of 4 years after baseline blood collection[4]. All three previous studies adjusted for age, sex, smoking and some classical vascular risk factors, and there was no significant heterogeneity among their separate results ($\chi^2=0.1; P>0.1$). A combined analysis of them gives a risk ratio for coronary heart disease of 1.5 (95% CI, 1.1–2.1) for people with baseline C-reactive protein values in the top third compared with those in the bottom third. For the reasons described above, however, the relevance of this statistically significant association remains uncertain, and studies in populations with previous disease may be less directly relevant than community-based studies to the assessment of possible cause and effect relationships.

Garcia-Moll et al[13] also reported that plasma C-reactive protein values seemed higher in female than in male patients with chronic stable angina. It is not clear, however, to what extent this was due to the use of hormone replacement therapy (which can increase plasma C-reactive protein values[14]), as the highest C-reactive protein values in their study were recorded among women taking such regimens. There is also uncertainty about any important sex differences in plasma C-reactive protein values in the general population. Studies in the general German[13], Scottish[15], and English populations[6], which collectively involved more than 7000 individuals, observed no large sex differences in plasma C-reactive protein, in contrast with a large American study which did so[16] (although that study did not report any adjustments for obesity and smoking).

Thus, as the amount of information on C-reactive protein and chronic diseases in different settings continues to increase, what should chiefly be emphasized is not the results in one or another particular study, but the totality of evidence, with due regard for the strengths and limitations of studies in healthy populations and those in sick populations.

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References


