The renaissance of C reactive protein

It may be a marker not only of acute illness but also of future cardiovascular disease

C reactive protein (CRP) has traditionally been used as an acute phase marker of tissue injury, infection, and inflammation, but the use of high sensitivity assays has recently shown that increased C reactive protein values predict future cardiovascular disease.

The C reactive protein response has no diagnostic specificity, but serial measurements can be helpful in clinical management. It is a powerful screening test for organic disease and is useful in monitoring known infectious or inflammatory diseases and their response to treatment.[1] Although a high value is unequivocal evidence of tissue damaging disease, C reactive protein values (unlike most other clinical laboratory tests) can really only be interpreted when all other clinical and laboratory information is available. Nevertheless, serial measurements of C reactive protein, added to the full clinical picture, contribute usefully to diagnosis, prognosis, and management.[1]

C reactive protein is a trace protein in healthy subjects, with a median concentration of around 1 mg/l, but values can exceed 400 mg/l in the acute phase response. Routine applications in adult medicine require measurement above 5-10 mg/l, but the development of high sensitivity assays has recently allowed clinicians to explore the role of C reactive protein in atherosclerotic disease.

Predictor of coronary events

Increased C reactive protein values significantly predict coronary events in outpatients with stable or unstable angina[2] and in hospital patients with severe unstable angina[3] and predict outcome after coronary angioplasty.[4] Even in healthy asymptomatic people in the general population individuals with baseline C reactive protein values in the top third of the distribution (geometric mean 2.4 mg/l) have twice the future risk of a coronary event than with those with values in the bottom third (mean 1.0 mg/l).[5] Similar relationships exist for stroke and peripheral vascular disease.

C reactive protein values increase with smoking and body mass index but the association with coronary events remains after adjustment for these potential confounders. The same is true for some other inflammatory markers, suggesting an association between inflammation and atherothrombosis. Inflammation is a central component of atherogenesis and is important in plaque instability and rupture, leading to thrombosis. However, it is not known whether increased C reactive protein production reflects arterial inflammation or inflammation elsewhere in the body. Chronic low grade infections may be risk factors for coronary heart disease, but C reactive protein concentrations do not correlate with serological markers of *Helicobacter pylori* or *Chlamydia pneumoniae* infection in the general population.[5]

In contrast, the association between C reactive protein values and body mass index probably reflects the importance of adipose tissue as a source of baseline circulating interleukin-6, the main cytokine mediator of increased C reactive protein production.[6] Increased C reactive protein values within the normal reference range may thus reflect mass of adipose tissue rather than actual inflammation. The question also arises of whether C reactive protein itself might contribute to atherothrombosis.

A pathogenetic role?

C reactive protein selectively binds to low density lipoprotein, particularly the partly degraded low density lipoprotein found within atherosclerotic plaques, and is generally present together with it, and activated complement, within such plaques.[7 8] Bound C reactive protein activates complement, is proinflammatory, and may thus contribute to atherogenesis. C reactive protein may also increase macrophage production of tissue factor,[9] the coagulation initiator responsible for occlusive thrombotic events. However, it will be possible to test whether C reactive protein has a pathogenetic role only when drugs are developed that selectively inhibit C reactive protein production or binding. Meanwhile, it is of interest that statins lower C reactive protein values,[10] suggesting that some of their protective effects may be mediated through suppression of inflammation or cytokines.

In contrast to the uncertain role of C reactive protein in the artery wall, there is strong evidence that C reactive protein increases ischaemic myocardial damage. C reactive protein production increases in all patients with myocardial infarction, peaking at about 50 hours, and high values are associated with a poor short term and long term prognosis. All fatal acute infarcts contain C reactive protein alongside activated complement,[11] and in experimental studies complement activation contributes importantly to infarct size. It has now been confirmed that human C reactive protein, via its capacity to activate complement, greatly increases infarct size after experimental coronary artery ligation,[12] and this presumably also happens in patients.

A spur to research

Routine empirical measurement of C reactive protein is a valuable aid to patient management across a broad range of clinical practice. Sensitive C reactive protein assay may become a new risk assessment marker for cardiovascular disease, and guidelines for its application are under discussion. While the potential management implications of a raised C reactive protein value in asymptomatic subjects are not yet clear, in those with active coronary disease a raised value definitely identifies a high risk group likely to require interventions. The possibility that C reactive protein may contribute to pathogenesis of atherothrombosis, and the fact that it increases ischaemic myocardial injury, should spur the development of specific drugs to inhibit C reactive protein.

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Finally, it is intriguing to wonder whether the excellent correlation between plasma C reactive protein concentrations and disease activity reflects not just the acute phase response to the original underlying pathological process, but also the capacity of C reactive protein to exacerbate existing tissue damage: possibly the more C reactive protein you produce, the sicker you get.

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MBP has received fees for speaking and consulting about C reactive protein from Abbott Laoratories and for speaking from Dade-Behring and has collaborated on C reactive protein testing with Roche Diagnostics.

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"Normal" blood glucose and coronary risk

Dose response effect seems consistent throughout the glycaemic continuum

Papers p 15

Although diabetes is a strong risk factor for coronary heart disease, the association between glycaemia within the "normal range" and coronary heart disease has been somewhat controversial.[1] A 1979 collaborative report from 15 countries found the risk ratio in the highest versus the lowest centile of glycaemia to range from 0.34 to 6.07 in men from Finland, Denmark, France, the United Kingdom, and the United States.[2] In other cohort studies, including Whitehall[3] and Framingham,[4] there appeared to be a threshold effect, with risk observed only at glucose levels approaching or including current diagnostic criteria for diabetes. There are several possible reasons for these contradictory results, including: the failure to exclude people with diabetes from the cohorts, compatible with a threshold effect; the multifactorial aetiology of coronary heart disease, compatible with confounding; or the large intra-individual variation in glucose (especially postchallenge glucose) values, compatible with misclassification bias.

Glycosylated haemoglobin, an integrated estimate of glucose over the preceding 6-12 weeks, provides a more reliable estimate of usual glycaemia, and should, therefore, be a more precise predictor of coronary heart disease risk. An elegant study by Khaw et al in this issue shows that glycosylated haemoglobin levels are positively associated with the risk of future coronary heart disease in a linear stepwise fashion, with no evidence of a threshold effect and independent of other common risk factors for coronary heart disease (p 15).[5] These are the most convincing data available that the association between glucose and coronary heart disease occurs throughout the normal range of glucose.

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Shifting the curve

The finding is important. An association between glycaemia and coronary heart disease in people who do not meet current criteria for a diagnosis of diabetes implies that glucose control for coronary heart disease prevention should begin in those with impaired glucose tolerance, and, as the authors note, points to the desirability of shifting the entire population glycaemia curve to the left. All modifiable risk factors that are continuous variables blur the line between treatment and prevention and lead to the selection of candidates for intervention on feasible and affordable rather than optimal grounds.

There is as yet no trial evidence that improved glucose control will reduce the risk of coronary heart disease among people without diabetes. Even in those with diabetes, the benefits have not been dramatic. In the 1960s the University Group Diabetes Program (UGDP) found a (still unexplained) increased cardiovascular risk in the group treated with tolbutamide, and no difference in cardiovascular disease outcomes between groups assigned to placebo, insulin standard (designed to have little or no effect on glycaemia), or insulin variable (which reduced glucose levels to 7-8 mmol/l).[6] In a study of young people with type 1 diabetes, the Diabetes Control and Complications Trial (DCCT), there were few cardiovascular events and the (non-significant) 40% reduced rate could have been due to chance.[7] The United Kingdom Prevention of Diabetes Study (UKPDS) of older adults