Soluble adhesion molecules in ischaemic heart disease

See page 1039 for the article to which this Editorial refers.

There is increasing evidence that atherosclerosis, the underlying cause of coronary heart disease, has an inflammatory pathogenesis. It has been known for some time that levels of inflammatory markers are elevated during acute coronary syndromes, and may indicate a poor outcome. More recently, large prospective epidemiological studies have found evidence that the development of atherosclerotic complications in apparently healthy individuals may be predicted by small elevations of inflammatory indices, presumably due to the indices reflecting underlying inflammatory activity of the disease. Thus, a meta-analysis of 19 prospective studies indicated that individuals with a single leukocyte count in the top third had a combined risk ratio for coronary heart disease of 1.4 vs those in the bottom third. Similarly, comparison of C-reactive protein values at baseline in the top third with those in the bottom third yielded a combined risk ratio of 1.7 for the development of coronary heart disease.

Early in atherosclerotic lesion formation leukocytes extravasate through the endothelium into the arterial wall. This process involves interactions between an array of cellular adhesion molecules, including the selectins (E-, P-, and L-selectin), the \( \beta_2 \) and \( \alpha_4 \) integrins (e.g. LFA-1, Mac-1, VLA-4) and members of the immunoglobulin superfamily (e.g. intercellular adhesion molecule-1 and vascular cell adhesion molecule-1). Evidence for the functional importance of these molecules in atherosclerosis comes from recent work with knockout mice, with those deficient in P-selectin or intercellular adhesion molecule-1 developing fewer fatty streaks and those deficient in both E- and P-selectin having fewer advanced atheromatous lesions. An E-selectin polymorphism mediating increased cellular adhesion has been found to be associated with premature coronary disease, possibly providing a corollary for these observations in the human population.

Since expression of the adhesion molecules E-selectin, P-selectin, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 are tightly regulated by inflammatory cytokines, their measurement provides an opportunity for determining the presence and activity of inflammation in different diseases. Although it is difficult to measure the cellular expression of adhesion molecules without obtaining tissue, quantifying the soluble forms in plasma provides an indirect approach. However, circulating levels of different soluble adhesion molecules are not necessarily simultaneously raised in inflammatory diseases. For example, we have found that in systemic lupus erythematosus the rise in soluble vascular cell adhesion molecule-1 greatly exceeds that of soluble intercellular adhesion molecule-1, whilst patients with active rheumatoid arthritis tend to have raised levels of either soluble intercellular adhesion molecule-1 or soluble vascular cell adhesion molecule-1 but seldom both. It is therefore possible that soluble intercellular adhesion molecule-1 and soluble vascular adhesion molecule-1 are markers of different facets of inflammatory disease.

In an asymptomatic population, soluble intercellular adhesion molecule-1 shows promise as a predictor of myocardial infarction on the basis of two independent prospective epidemiological studies. In this setting soluble vascular cell adhesion molecule-1 and sE-selectin appear not to be independent risk factors, whilst sP-selectin has yet to be evaluated in a prospective study. Measuring soluble adhesion molecules may also help predict poor outcome after intervention. For example, sE-selectin levels have previously been shown to predict those who have restenosis after femoropopliteal angioplasty. The paper by Wallén et al. in this issue adds to the knowledge of the associations of adhesion molecules and inflammation to cardiovascular risk by suggesting that soluble intercellular adhesion molecule-1 and soluble vascular cell adhesion molecule-1 predict coronary events in patients with chronic stable angina.

There are reasonable grounds therefore for believing that measuring levels of soluble adhesion molecules may be helpful for predicting patient outcome in clinical cardiology. However, even the largest trials of adhesion molecules to date have only involved 400 patients, allowing type I and/or type II errors to occur due to chance. There is a need therefore for larger prospective studies, in order to establish which, if any, soluble adhesion molecules offer added value to the risk stratification produced by the well-known coronary risk factors and standard inflammatory markers.

Finally, it is tempting to conclude that soluble adhesion molecules report directly on inflammation within arteries. However, it is equally possible that the inflammation leading to adhesion molecule release is at distant sites, and that a shift in thrombotic balance as a consequence of inflammation is what determines the risk of myocardial infarction.
or death. Determining whether or not levels of soluble adhesion molecules reflect cellular events in atherosclerotic plaques will need to await technical developments for imaging the activity of arterial inflammation directly.

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References

Is a low fat diet enough to achieve serum cholesterol goals?

See page 1020 for the article to which this Editorial refers

The prevalence of coronary heart disease has been shown to be correlated to the level of serum total and low density lipoprotein (LDL) cholesterol as well as inversely correlated to high density lipoprotein (HDL)[1]. In a recent analysis of primary and secondary prevention trials, cholesterol-lowering drug studies showed a significant reduction in coronary heart disease mortality and in total mortality[2]. It is assumed that reductions in serum LDL cholesterol level produced by dietary therapy will have similar effects[3,4]. The overall importance of coronary heart disease in terms of morbidity, mortality and economic cost is immense in Western countries. Diet modification and dietary advice as intervention measures were perceived to be safe and effective and proved attractive to government bodies[1]. American guidelines[3,4] for managing patients with high serum cholesterol concentrations concur that diet is of prime importance in the management of the condition, and advocate, as initial treatment, the National Cholesterol Education Program step 1, or general lipid-lowering diet (less than 30% total fat, less than 10% saturated fat, and less than 300 mg of cholesterol per day). The more intensive National Cholesterol Education Program step 2 diet (less than 30% total fat, less than 7% saturated fat, and less than 200 mg of cholesterol per day) is recommended if the National Cholesterol Education Program step 1 diet proves insufficient, or for the secondary prevention of coronary heart disease. Similarly, recent European recommendations[5] advocate for secondary prevention of coronary heart disease to reduce total fat intake to 30% or less of total energy intake, the intake of saturated fat to no more than one-third of total fat intake, and the intake of cholesterol to less than 300 mg per day. There have, however, been few randomized controlled trials of intensive dietary therapy in outpatients with hypercholesterolaemia[6] and so the efficacy of dietary therapy has not been defined. Many of the previous studies (see below) of lipid-lowering diets have been conducted in institutional settings or under metabolic-ward conditions, in which adherence to a diet can be ensured[7]. Furthermore, the diet recommended for reducing LDL cholesterol levels...