

COMMENTARY

The association between elevated levels of inflammation biomarkers and coronary artery disease and death

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In this issue of the Journal, Lee and colleagues report on the associations between 3 plasma markers of low-grade inflammation — C-reactive protein (CRP), interleukin (IL)-6 and serum amyloid A protein — and total homocysteine with coronary artery disease (CAD) and death in a Canadian angiography cohort of 1117 patients followed for 8.5 years.¹ They found no significant associations between elevated levels of these biomarkers and CAD, but they did find significant independent associations of elevated IL-6 (a key pro-inflammatory cytokine) and homocysteine levels with both CAD-related and all-cause death. Their study is of considerable interest because in the current wave of enthusiasm for measuring such biochemical risk factors for CAD and other types of cardiovascular disease,² many believe that inflammation biomarkers and homocysteine play direct causal roles in the development of CAD (e.g., by promoting vascular wall damage and thrombosis). Many also believe that these biomarkers are specific for cardiovascular risk, and that high levels indicate additional cardiovascular preventive measures.

Although current US guidelines recommend consideration of measurement of CRP³ and homocysteine⁴ levels as part of routine individual risk factor screening and management in cardiovascular prevention, several international commentators — myself included⁵ — have challenged the underlying, unproven hypotheses that such markers play a causal role in cardiovascular disease, that they add significantly to the established predictive value of current clinical scores such as the Framingham score, and that their measurement reduces cardiovascular risk by motivating patients to follow lifestyle advice or by indicating additional medical interventions.⁵⁻⁷

Association with CAD

Lee and colleagues report that “classical” risk factors currently used in CAD risk prediction (age, male sex, smoking status, diabetes, waist circumference, total cholesterol:high-density lipoprotein cholesterol ratio), as well as triglyceride and apolipoprotein B levels, were significantly associated with CAD. These findings are entirely consistent with those of many previous necropsy and angiographic studies. In contrast, CAD (which Lee and associates defined as the presence of any lesion with stenosis greater than 10%) was not signifi-

cantly associated with elevated plasma levels of CRP, IL-6, serum amyloid A protein or homocysteine. These findings do not support the hypotheses that these biomarkers play a causal role in atherogenesis. The importance of this study is that, to my knowledge, no previous studies have examined such associations in a large, prospective angiographic cohort in which CAD was defined using sensitive criteria.

When Lee and colleagues used the definition of CAD as the presence of any lesion of 50% stenosis (which was developed for assessing suitability for cardiac surgery or angioplasty), they observed significantly higher CRP and IL-6 levels in the CAD group. However, the data are not presented in the paper, and nor is the multivariate analysis reported to assess the degree to which these associations were attributable to confounding by their mutual relations to classical risk factors.⁵ It would be of considerable interest not only to report such analyses of baseline data in coronary angiographic cohort studies but also to study, by multivariate analysis, the associations of these markers as CAD progresses using repeat coronary angiography; however, the ethical and logistic problems in repeating this invasive procedure limits the feasibility of such studies.

In the Edinburgh Artery Study, we have recently reported an alternative approach to assessing the association of elevated plasma levels of inflammation and hemostatic biomarkers and homocysteine with progressive atherosclerosis. Peripheral arterial stenosis in the lower limbs using the ankle-brachial index, the assessment of which, being noninvasive, is readily repeated in cohorts randomly selected from the general population, is correlated with the extent of coronary and carotid atherosclerosis; because atherosclerosis in the arteries supplying the lower limbs is much more extensive than that in the coronary or cranial arterial systems, it may be more likely to be associated with circulating levels of biomarkers. Consistent with the findings of Lee and colleagues and the previous studies of CAD quoted in their paper, we observed that elevated CRP and IL-6 levels were significantly correlated with the extent of stenotic peripheral atherosclerosis; in addition, we observed that elevated IL-6 (rather than CRP or homocysteine) levels at baseline were significantly associated with progression of atherosclerosis over a 12-year follow-up, using multivariate analysis that included the baseline ankle-brachial index, cardiovascular risk factors and cardiovascular disease at baseline.⁸

Although these findings may be consistent with a hypothetical causal role for IL-6 in the progression of atherosclerosis and hence in cardiovascular disease, proof of causality requires further observational studies, randomized trials of long-term selective reduction in inflammation biomarkers and homocysteine, and meta-analyses of such studies. In the meantime, “Mendelian randomised trials” of functional polymorphisms that influence plasma levels of CRP,¹⁰ homocysteine¹¹ or fibrinogen¹² have shown little or no association with the risk of CAD, which does not support their postulated causal roles.

Association with death

The authors report that, in their angiographic cohort, elevated levels of inflammation biomarkers and homocysteine were similarly related to all-cause and CAD-related death. These findings are consistent with those from general population cohorts, in which the association of elevated plasma levels of inflammation biomarkers such as fibrinogen^{5,9} and CRP⁵ are at least as strong for all-cause death as for CAD-related death. Such nonspecificity is further evidence against a causal role.⁵ Instead, their association with cardiovascular events may be largely due to confounding by multiple adverse environmental risk factors or perhaps because, in a case of “reverse causality,” arterial lesions contribute directly to systemic levels of inflammation biomarkers.⁵ The finding of no significant association of plasma biomarkers with early atherosclerosis along with their significant association with all-cause death in the same cohort provides further evidence that elevated levels of such markers may reflect the cumulative effects of an adverse environment on the nonspecific inflammatory response and, perhaps, on related biological pathways that thereby promote death through a variety of mechanisms, including cardiovascular, malignant and infectious disease, as part of “biological aging.”¹⁵

Lee and colleagues also found that elevated total homocysteine levels were as strong an independent predictor of all-cause death (as well as CAD-related death) as were elevated IL-6 levels. Although it has been postulated that elevated homocysteine levels may promote vascular inflammation,¹³ the association of homocysteine levels with CAD appears to be independent of IL-6, CRP and fibrinogen levels.¹⁴ The recent Homocysteine Studies Collaboration meta-analysis of the relations between blood homocysteine levels and risk of CAD and stroke did not analyze all-cause mortality or noncardiovascular mortality.¹⁵ In light of the study by Lee and colleagues, emerging evidence that circulating homocysteine levels may not play a causal role in CAD,¹¹ and evidence that other “emerging” risk factors such as elevated fibrinogen and CRP levels show similar associations with cardiovascular and noncardiovascular mortality,^{5,9} the Homocysteine Studies Collaboration should be encouraged to perform similar analyses for homocysteine levels and risk of death.

Conclusions

The study by Lee and colleagues adds to increasing evidence that plasma levels of inflammation biomarkers and homocysteine are more strongly related to all-cause death than to CAD; in combination with other evidence, these results do not support the hypotheses that these biomarkers play any causal roles in the pathogenesis of cardiovascular disease. There is currently insufficient evidence to support the measurement of these markers as part of routine cardiovascular risk assessment in clinical practice.⁵⁻⁷

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