The Role of Inflammation in Cardiovascular Disease

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The article in this issue by Gusselkoo et al.,1 “C-reactive protein is a strong but nonspecific risk factor of fatal stroke in elderly persons,” demonstrates 2 important points. First, for maximum predictive value, a variable such as C-reactive protein (CRP) should preferably be a risk factor for a specific outcome rather than for a broad range of unrelated outcomes such as stroke, coronary heart disease, cancer, and total mortality. There are some risk factors such as cigarette smoking and radiation exposure that are associated with many different outcomes, and future work may show that CRP falls into this important category. However, in general, the specificity of an association is an important component, often reflecting a causal relationship. These investigators determined that elevated CRP is not specific for stroke or other cardiovascular disease mortality. This is not surprising, since an elevated CRP level is related to inflammation,2 and increased inflammation will be noted for many diseases, such as cancer, cardiovascular disease, infection, connective tissue diseases, injury, etc.

Second, the relationship between CRP and stroke or other causes of death was time dependent; ie, the shorter the time between the measurement of CRP and death, the higher were the levels of CRP. This finding is consistent with results in older individuals from the Cardiovascular Health Study3 but not with results in middle-aged or younger individuals, such as the follow-up of the Multiple Risk Factor Intervention Trial4 or the Physicians’ Health Study.5 In older surface in response to CRP.7 However, the association of elevated CRP may therefore be an important marker of evolving disease but not necessarily in the causal pathway. It is possible, however, that elevated CRP could be related to a specific pathophysiology, such as the risk of clotting and thrombosis that is part of the final common pathway, at least for cardiovascular disease. Possible mechanisms include the expression of tissue factor on the monocyte surface in response to CRP.7 However, the association of elevated CRP with multiple outcomes in this study would be most consistent with the position that this is not the case.

In younger and middle-aged individuals, CRP may be a measure of the evolving development of subclinical disease that is not identifiable by usual clinical measurement techniques. Years later, this evolving subclinical disease may lead to clinical disease. Thus, CRP again may not be in the causal pathway but rather a marker for the extent of unmeasured subclinical disease and its evolution over time. However, as above, there are possible mechanistic alternatives. Elevated CRP reflects an increased production of proinflammatory cytokines such as interleukin-6, which may be contributing to the pathophysiology of disease either directly8 or indirectly through their relationships to other important components of inflammation, thrombosis, or fibrinolysis.9,10

It would be imprudent to jump to the conclusion that CRP and related acute-phase proteins are mechanistic risk factors for disease and to assume that lowering the CRP level will reduce the risk of disease, without the appropriate evidence to support such a position. Although the study of CRP and other acute-phase proteins is of considerable importance, we should recognize that at the present time there is no direct evidence that CRP is an independent mechanistic risk factor for cardiovascular disease. There is also no evidence that it is in the causal pathway, and it does not appear to be a marker of disease extent or severity. Finally, there is certainly no evidence that lowering CRP, or any acute-phase protein, will reduce the progression of underlying disease or the risk of future disease events.

References

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