Dr. Skartlien and coworkers1 in this issue provide a very interesting correlation between dietary intervention with respect to triglycerides and the levels of the phospholipase C-sensitive factor VII related activity. This activity has previously been correlated with the risk of cardiovascular disease. The observations in this paper suggest a direct relationship between a coagulation activity and a dietary lipid-related response. Previously, factor VII clotting activity levels per se have in some,2-4 but not all,5 studies been correlated with cardiovascular risk. Potentially, the lipid dependence of the factor VII-related activity may be a significant factor in resolving the differences among the observations made by various laboratories.

The phospholipase C-sensitive form of factor VII clotting activity was initially reported by Oesterud and coworkers.6 This activity is enhanced in pregnant women,7 in men at high risk for cardiovascular disease,8 and in male survivors of acute myocardial infarction.9 The previous correlations of this activity with cardiovascular disease, when combined with the dietary alterations presented in the present study, indicate that the nature of the activity and the mechanism of its expression require further basic, clinical, and epidemiological studies.

It is interesting that the activity correlates with the triglyceride lipid fraction, since triglycerides are not substrates for phospholipase C. This enzyme hydrolyzes phospholipids to remove the phosphate ester and produce diacylglycerol. Further, phospholipids, and not triglycerides, support the formation of the coagulation enzyme complexes.10,11 Phospholipid components are essential constituents of the complex catalysts associated with all of the vitamin K-dependent zymogen-enzyme conversions.12 Studies by Giles and coworkers12 have demonstrated significant thrombotic risk associated with coagulant active phospholipids in the presence of small amounts of factor Xa. While not procoagulant in their own right, triglycerides can influence the physical state of other membrane lipids. Triglycerides, while not established risk factors in atherogenesis, are loosely associated with increased risk of cardiovascular disease.13,14 These lipids have been shown to be correlated with increased levels of plasminogen activator inhibitor.15

Factor VII can potentially exist in at least five forms: the uncleaved, single-chain form of the protein (factor VII); the cleaved, active form (factor VIIa); either form in complex with tissue factor/phospholipid/Ca ++; and factor VIIa in a complex with tissue factor/phospholipid/Ca ++/factor Xa and the lipid-associated coagulation inhibitor.16,17 There is not unanimity of opinion with regard to the question of inherent activity proposed to exist in uncleaved factor VII.18,19,20 Further, it is unclear to what degree each of the factor VII/VIIa species contributes to any particular clot endpoint bioassay. It is clear, for example, that coagulation assays are highly sensitive to the chemical nature, physical state, and concentration of the lipids used.

Since the association of cardiovascular disease risk with factor VII levels measured in coagulation assays may depend upon the assay technique employed and the nature of the thromboplastin (phospholipid-tissue factor preparation) used, it appears essential to develop explicit descriptions of the nature of the factor VII-related activity measured and shown to be correlated with cardiovascular risk in the present and other studies. Basic studies of factor VII/VIIa interactions will be required to provide a mechanistic interpretation of assay performance in terms of sensitivity and specificity. The quantitative influence of various related plasma constituents upon the measured activity must be evaluated.

The present study should lead us to explore in depth the intimate relationship between dietary lipid intake, blood lipids, clotting factor activities, and cardiovascular disease. The studies also illustrate the need to develop assay standardization procedures. Discussions comparing the results of different epidemiological studies should take into account not only the clinical study design and the population studied, but also the detailed nature of the assays performed. Finally, it should be emphasized that studies that demonstrate the association of cardiovascular disease with clotting factor elevations illustrate correlations and not causality.
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