Pregnancy-Associated Plasma Protein A as Predictor of Outcome in Patients With Suspected Acute Coronary Syndromes

We read with interest the article by Lund et al on circulating pregnancy-associated plasma protein A (PAPP-A) in 136 patients evaluated for suspected acute coronary syndrome without cardiac troponin I elevation. PAPP-A concentrations above 2.9 mIU/L during the first 24 hours independently predicted cardiovascular death, nonfatal myocardial infarction, or revascularization over the following 6 months. The risk ratio of PAPP-A >2.9 mIU/L, adjusted for C-reactive protein (CRP), age, gender, diabetes, current smoking, hypertension, previous myocardial infarction, and congestive heart failure was superior to that of CRP >2 mg/L: 4.6 for PAPP-A (95% confidence interval 1.8 to 11.8, \( P = 0.002 \)) versus 2.6 for CRP (95% confidence interval 1.1 to 6.5, \( P = 0.03 \)). The cumulative risk of an event, graded by increasing PAPP-A values, was 8% in the lowest group and 37.9% in the highest (\( P = 0.0012 \)). PAPP-A and CRP levels were independent of each other (\( r = -0.03, \) \( P = 0.7 \) on admission; \( r = 0.02, \) \( P = 0.8 \) for peak values). These striking data are discussed only briefly by the authors, who, despite showing a lack of correlation between PAPP-A and CRP, propose PAPP-A as a mediator of the inflammatory reactions that would lead to plaque rupture and clinical instability.

We would like to propose an alternative interpretation, based on the main activity of PAPP-A, which is to cleave insulin-like growth factor-1 (IGF-1) from its binding protein-4, thereby increasing the accessibility of free IGF-1 to tissues. Several lines of evidence indicate that PAPP-A is induced in response to, and within, damaged tissues, as a promoter of repair, in virtue of its IGF-1-dependent actions on vasculogenesis, vasodilation, cell preconditioning, cell survival, and insulin-sensitivity. Even mild damage, such as brief ischemia, would activate this pathway, thus explaining the higher sensitivity of PAPP-A compared with cardiac troponins as predictors of outcome. In response to necrosis, the broad-ranging fluctuations of PAPP-A justify its correlation with inflammatory markers. The remission of rheumatoid arthritis and other inflammatory states during pregnancy (the prototype of increased IGFs) and inflammatory markers. The remission of rheumatoid arthritis and other inflammatory states during pregnancy (the prototype of increased PAPP-A) denotes PAPP-A as a suppressor, rather than mediator, of inflammation and tissue damage.

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Response
We thank Drs Conti, Andreotti, and Zuppi for showing their interest in our article on the value of pregnancy-associated plasma protein A (PAPP-A) in acute coronary syndromes (ACS). In this reply, we further clarify the tentative role of PAPP-A in atherosclerosis and the inflammation cascade.

As we know, inflammation contributes importantly to every stage of the development of the atherosclerotic plaque. Insulin-like growth factor (IGF)-1 binds to the type I IGF receptor (IGF-1R), which is present on many cell types found in the plaque. However, the outcome of IGF action on different cells relates to other molecules and a complex microenvironment.

In macroglyphs, IGF promotes excess low-density lipoprotein cholesterol uptake, release of proinflammatory cytokines, and chemotaxis. This inflammatory environment digests the fibrous cap, leaving the plaque vulnerable to rupture. PAPP-A cleaves IGF binding protein-4 and -5 in vitro and may function similarly in vivo to enhance local IGF bioavailability. Recently, it has been demonstrated that PAPP-A expression is significantly enhanced by inflammatory cytokines such as tumor necrosis factor-alpha in adult human fibroblasts. If the same is found to be true in atherosclerotic plaques, increased PAPP-A will further increase levels of local bioactive IGF, thereby causing the plaque to proceed to disruption unless the chain of reactions is interrupted.

IGF-I has a chemoattractive action on vascular endothelial cells and induces endothelial tube-forming activity in vitro. However, the ultimate outcome may be different because of the interactions between various bioactive molecules and cells within the atherosclerotic lesion. A recent study shows that a long-term low dose of IGF-1 significantly enhances tumor necrosis factor-alpha-induced adhesion molecule expression in endothelial cells, suggesting that IGF-1 is an enhancing factor for cytokine-induced endothelial cell inflammation.

In vitro IGF-I plays an important role in migration, cell cycle progression, and survival of vascular smooth muscle cells. However, there are studies showing that human plaque-derived vascular smooth muscle cells in vivo are not responsive to the protective effects of even high levels of IGF-1 because of reduced IGF-1R expression and increased insulin-like growth factor binding protein synthesis, which can be caused by oxidized low-density lipoprotein, one of important players in plaque inflammation.

The results of our study support at least indirectly the view that PAPP-A (either alone or via IGFs) is a mediator of the adverse inflammatory events which promote atherogenesis. Thus, although we cannot refute the possibility, as suggested by Drs Conti, Andreotti, and Zuppi, our interpretation has been different. One should be cautious before drawing any definite conclusions from blood levels of biomarkers on what exactly is happening on the tissue level. Clearly, further studies are needed to prove the exact role of PAPP-A in atherosclerosis and its complications.

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