Pregnancy associated plasma protein-A and coronary atherosclerosis: marker, friend, or foe?

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Online publish-ahead-of-print 1 September 2005

This editorial refers to 'Relationship among pregnancy associated plasma protein-A levels, clinical characteristics, and coronary artery disease extent in patients with chronic stable angina pectoris'† by J. Cosin-Sales et al., on page 2093

The natural history of coronary artery disease is complex and is characterized by the central role played by inflammation. Atherogenic stimuli, such as oxidized lipoproteins, glycated end products, hypertension, and smoking, cause endothelial dysfunction and apoptosis, vascular expression of adhesion molecules, and recruitment of inflammatory cells, which then migrate in the intima, thus setting the stage for plaque formation.1 Coronary atherosclerotic plaques have a high prevalence in the population, even in subjects dying of non-cardiac causes, and their burden increases with age.2 In many subjects these plaques remain silent for life; in others they suddenly become thrombogenic, triggering occlusive or subocclusive thrombosis, responsible for acute coronary syndromes. In survivors of a first acute coronary event, the latter is followed by a period, lasting about 1 year, of enhanced risk of new acute ischaemic events. Thereafter, the disease enters a new phase of quiescence, which can last for years. In a sizeable proportion of patients, the brisk transition from coronary stability to instability is associated with a sudden and widespread activation of inflammatory cells, detectable in the entire coronary circulation, in the myocardium and, in a subset of patients, even in remote arterial districts.3,4 This inflammatory outburst is not explained by the atherosclerotic burden, by activation of the haemostatic system, or by ischaemia.1 Thus, inflammation appears to play a key part, not only in plaque growth, but also in plaque disruption. However, studies based on circulating levels of C-reactive protein, a prototypic marker of inflammation, while uniformly supporting the latter notion, have failed to show a consistent and close relation between C-reactive protein and extent of coronary artery disease. Therefore, there is room for exploring novel potential biomarkers of coronary atherosclerosis and, in particular, the possible role of endocrine-based systems.

Cosin-Sales et al.5 report on a cohort of 643 stable patients undergoing coronary angiography in a tertiary centre for chest pain evaluation. The authors assess the predictive value of both serum pregnancy associated plasma protein-A (PAPP-A) and C-reactive protein for the presence and extent of obstructive coronary disease. PAPP-A levels were found to be higher in patients with multi-vessel disease than in those with single-vessel disease, and higher in the latter than in patients without obstructive disease. Notably, a concentration >4.5 mIU/L was found to predict the presence of significant (>50%) stenoses with a sensitivity of 45% and a specificity of 84%. In contrast, as in several (but not all) previous studies, C-reactive protein failed to predict both the presence and the extent of disease. This interesting article suggests, for the first time, that the measurement of PAPP-A may become a clinically useful tool in stable patients with chest pain, both to diagnose, or exclude, and to gauge the extent of obstructive coronary lesions, although further studies will be necessary to establish the reproducibility and cost-effectiveness of such a non-invasive strategy, compared with one based solely on stress ECG or imaging. Several assays to measure PAPP-A in biological fluids are now available, including an ultrasensitive test, but their validation, particularly in the setting of cardiovascular diseases, warrants further investigation.6 In their article, Cosin-Sales et al.5 clearly discuss the practical implications of their findings. The authors also suggest that PAPP-A might be a pathogenetic agent in coronary atherosclerosis. This editorial will expand the authors’ discussion on the possible role played by PAPP-A in ischaemic vascular diseases.

PAPP-A is a large, zinc binding proteinase produced by different cell types, including fibroblasts, vascular smooth muscle cells, and male and female reproductive tissues (placental trophoblast, ovarian follicules, Leydig cells).6,7 It circulates either as an active homodimer or covalently bound to, and inhibited by, the proform of eosinophil major basic protein. PAPP-A specifically degrades insulin-like growth factor binding proteins (IGFBPs)-4 and -5, thereby allowing active IGF-1 to bind to cell-surface Type 1 IGF receptors.7 IGF-1 is a small, 7.5 kDa peptide, highly homologous to insulin, with glucose-lowering effects. It stimulates cell proliferation and differentiation. At least six different soluble IGFBPs bind IGF-1 with high affinity (similar to or greater than IGFBP-3), and are involved in the regulation of IGF-1 bioactivity.8,9 PAPP-A specifically complexes with IGFBP-3, resulting in diminished bioactivity of IGF-1.

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than Type 1 IGF receptors), thereby tightly regulating IGF-1’s bioavailability.\textsuperscript{7,8} The proteolytic degradation of the IGFBPs is considered the predominant mechanism for the release of bioactive IGF-1. At least six different IGFBP-proteases, including PAPP-A, have been identified.\textsuperscript{7}

Both PAPP-A and IGF-1 are commonly referred to as potential proatherosclerotic and plaque destabilizing factors. In the past few years, several studies have documented raised plasma PAPP-A in patients with acute coronary syndromes, associated with a worse short- and medium-term outcome.\textsuperscript{9} PAPP-A is reported to be secreted by activated macrophages in the atherosclerotic plaque and to contribute to plaque disruption in virtue of its being a protease;\textsuperscript{5} yet, beyond its degradation of IGFBPs-4 and -5, no other proteolytic action has so far been attributed to PAPP-A.\textsuperscript{7} IGF-1 has been considered a mediator of plaque growth through induction of cell proliferation. Moreover, in vitro, IGF-1 has been reported to induce activation, chemotaxis, LDL cholesterol uptake, and release of proinflammatory cytokines by macrophages, which could contribute to plaque growth and disruption.\textsuperscript{5} Yet, a large body of recent clinical and experimental evidences suggests that IGF-1 may instead provide protection against ischaemic vascular diseases.

Indeed, reduced circulating IGF-1 levels have been independently associated with coronary artery disease, carotid intimal-medial thickness and the metabolic syndrome in cross-sectional studies, and with the development of glucose intolerance, myocardial infarction, heart failure, or cardiovascular death in large prospective studies.\textsuperscript{10} Advancing age and the presence of virtually all the traditional cardiovascular risk factors have been associated with reduced circulating IGF-1 levels.\textsuperscript{8,10} Moreover, clinical and laboratory data indicate that IGF-1 preserves insulin sensitivity, endothelial function, microvascular function, and plaque stability, while exerting antiapoptotic, K\textsuperscript{+} channel-opening, anti-inflammatory, antioxidant, and cardioprotective effects.\textsuperscript{8,10} The molecular mechanisms underlying these actions are beginning to emerge. Human endothelial and vascular smooth muscle cells possess high-affinity receptors for IGF-1 that mediate the activation of the phosphatidylinositol-3 and Akt kinase signalling cascades which lead to constitutive nitric oxide formation, with its attending vasodilator, antplatelet and insulin-sensitizing actions.\textsuperscript{10} Finally, both IGF-1 and nitric oxide promote endothelial progenitor cell mobilization\textsuperscript{11} and IGF-1 stimulates endothelial cell migration, proliferation, and regeneration, while inhibiting endothelial and vascular smooth muscle cell apoptosis.\textsuperscript{10,11} The latter effects are likely to prevent both plaque formation and disruption.\textsuperscript{10,11}

As IGF-1 appears to be cardioprotective, raised PAPP-A, by enhancing IGF-1 bioavailability, should also offer cardiovascular protection. How then can we solve the conundrum determined by the observation that raised PAPP-A levels, but reduced IGF-1 levels, are both associated with increased cardiovascular risk? One possible answer is that raised PAPP-A may be reactive to, and not causal of, vascular and myocardial damage, as part of a compensatory, IGF-1 mediated, reparative, antiapoptotic, antisenescent, survival pathway.

In conclusion, the article by Cosin-Sales et al.\textsuperscript{5} shows that PAPP-A is a potentially clinically relevant marker of the presence and extent of coronary atherosclerosis. However, to define PAPP-A’s exact pathogenetic role in plaque growth and disruption may be too soon. To better understand the meaning of PAPP-A in arterial disease further actions are warranted, which might include: (1) the validation of a standardized and sensitive assay for its measurement; (2) the study of PAPP-A’s interaction with IGF-1, within the multiple mechanisms that regulate IGFBP proteolysis; (3) the investigation of the combined prognostic role of both PAPP-A and IGF-1 in large epidemiological studies in asymptomatic subjects and in patients with established coronary artery disease.

Conflict of interest: none declared.

References