Inflammatory and coagulative markers of atherosclerosis

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This editorial refers to 'Albuminuria as risk factor for initiation and progression of carotid atherosclerosis in non-diabetic persons: the Tromsø Study'† by L. Jørgensen et al., on page 363 and 'Inflammatory, haemostatic, and rheological markers for incident peripheral arterial disease: Edinburgh Artery Study‡ by I. Tzoulaki et al., on page 354

Many markers associated with atherosclerosis have been identified in the last 50 years. Some of them act as factors, both mathematically (factors = risk multipliers) and biologically (factors from the latin facient, producing), and others are mere indicators. Among the novel markers (Table 1), many are strictly connected with inflammation or coagulation. Some studies on these markers have been considered with suspect, because they were conducted on patients rather than on general population, because the number of subjects was low, or because the experimental design was inadequate. Nevertheless, the results of all studies are univocal and similar to those of population-based large-scale studies.1–5 Today there is, therefore, general agreement on the role of these novel markers. Although incertitude remains about the underlying pathophysiological mechanism, inflammation and haemostasis are considered as driving forces in the process of atherosclerosis.

There is evidence of inflammation in vascular atherosclerotic disease. Activated mast cells are present in human coronary atheromas as well as in the adventitia of coronary arteries of patients with variant angina, the CD3+/DR+ T-lymphocytes are more represented in variant than in stable angina, and inflammatory burden could be a consequence of the presence of a symptomatic carotid stenosis has been detected using high-resolution magnetic resonance imaging. More generally, inflammation and neangiogenesis play a central role in atherosclerosis and make the atherosclerotic process a continual evolving model. Sometimes (as in the case of subjects with Clamydia pneumoniae or periodontal disease), the inflammatory response to a well-determined infectious event turns out to be atherogenic, probably promoting a pro-atherogenic serum lipid profile. In other cases—the great majority—the link of atherogenesis with inflammation is uncertain or even merely presumptive.

Urinary albumin excretion (UAE) is an index of glomerular dysfunction and an independent predictor of atherosclerosis and its complications as well. The so-called microalbuminuria (UAE 30–300 mg/day or albumin-to-creatinine ratio 30–300 mg/dL) determined by sensitive techniques is even an earlier predictor. Carotid arteries have been commonly used to demonstrate this association simply because the supraortic district is more accessible to ultrasonographic techniques, and in this site plaques can be detected and measured with extreme precision. UAE is a continuous variable and should not be categorized. Jørgensen et al.6 just tackle this topic by analysing in a longitudinal perspective 4037 cases from general population after excluding those with diabetes or with known inflammatory disease. Their results, deriving from a very accurate phenotype, indicate that albumin-to-creatinine ratio, even far lower than the usual label of microalbuminuria, is associated with carotid plaque development. Nephropathy sustaining albuminuria must be, of course, a concomitant or an indicator, rather than the cause, of a general endothelial vascular dysfunction, but the mechanism of this association is uncertain, particularly in non-diabetic subjects.7 Early nephropathy actually correlates with atherosclerosis and its complications (in our general population, top vs. bottom serum creatinine, even in the normal range, increases by the risk of coronary death five-fold in elderly men).8 As a matter of fact, it may be difficult to clarify whether UAE, an expression of renal microcirculatory abnormality, acts as a marker of early nephropathy rather than of atherosclerosis per se. The link between these two conditions must be chronic low-grade inflammation. UAE correlates with fibrinogen, homocysteine, and C-reactive protein, shifting interest from kidney to inflammation/haemostasis or perhaps underlying the flogistic component of both early nephropathy and early atherosclerosis. Tzoulaki et al.9 in another longitudinal study among a great number of subjects also highlight inflammatory, haemostatic, and rheological biomarkers of incident vascular damage, namely, C-reactive protein, interleukin-6, fibrinogen, D-dimer, adhesion molecules, haematocrit, and blood viscosity.

The increasing evidence suggests that C-reactive protein and fibrinogen are useful in assessing cardiovascular risk. C-reactive protein has numerous atherogenic effects such as generation of oxygen radicals, clotting, expression of plasminogen activator inhibitor 1, and plaque destabilization. Out of acute occasional inflammation, high levels of high-sensitive C-reactive protein are a marker of vasospasm
and have also been related to increased risk, particularly in low-to-intermediate-risk subjects. C-reactive protein responds well to vitamin E, β-blockers, ezetimibe, angiotensin-converting enzyme inhibitors, angiotensin II receptor (AT1) antagonists, and glitazones, leading to possible angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and through a pro-oxidative action. However, decreasing the production of nitric oxide, by impairing endothelial integrity is not at all a surprise. SUA is associated with cardiovascular risk also after adjustment for other risk multipliers and first-line markers of cardiovascular risk. The list of these novel risk factors is largely incomplete. Those shown in Table 1 are indicative of subclinical organ damage or hidden arteriosclerosis of a degree insufficient to produce a clinical disease, but able to alter peripheral vessels and to increase cardiovascular events. In this perspective, they could allow early screening of those subjects who should be addressed to special surveillance or to stronger prophylaxis. Owing to ethical and economical considerations, it is therefore foreseeable that in the near future they all will end up being included in risk charts (as already proposed, for instance, for pulse pressure). Whether SUA actually contributes to the disease process or is a mere indicator is still object of debate. In our experience, SUA predicts coronary mortality in general population with a mere indicator is still object of debate. In our experience, SUA predicts coronary mortality in general population (Figure 1). Via URAT-1 renal protein, AT1-antagonists have uricosuric properties, a class-specific effect that could potentially be useful in subjects receiving these drugs for indications other than hyperuricaemia (more in general, AT1-antagonists also tend to inhibit inflammation, interleukins, and COX-2/mPGES-1 expression and as a consequence to stabilize atherosclerotic plaques).

In conclusion, several novel risk factors, very often related to inflammation or haemostasis, have come to the limelight in the last years and are currently considered risk multipliers and first-line markers of cardiovascular risk. The list of these novel risk factors is largely incomplete. Those shown in Table 1 are indicative of subclinical organ damage or hidden arteriosclerosis of a degree insufficient to produce a clinical disease, but able to alter peripheral vessels and to increase cardiovascular events. In this perspective, they could allow early screening of those subjects who should be addressed to special surveillance or to stronger prophylaxis. Owing to ethical and economical considerations, it is therefore foreseeable that in the near future they will all end up being included in risk charts (as already proposed, for instance, for pulse pressure).

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