Real or apparent ethnic differences in cellular adhesion molecule activity?

In this issue of Clinical Science, Miller et al. [1] present data on the associations between ethnicity and circulating levels of cellular adhesion molecules in subjects without cardiovascular disease or major conventional cardiovascular risk factors. The authors have described some interesting differences, with lower levels of soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1) and soluble P-selectin in black subjects, of Caribbean and West African origin, than in white individuals and individuals of South Asian origin all living within a small geographical area. These findings are of importance in suggesting possible mechanisms which could contribute to the observed differences in incidence of cardiovascular disease in different ethnic groups. However, some caution should be exercised in their interpretation.

Although much has been published on the associations between circulating levels of cellular adhesion molecules and the presence of cardiovascular risk factors, the presence of cardiovascular disease, the pathogenesis of acute coronary syndromes and the risk of future cardiovascular events, there are many apparent paradoxes amongst the data. Miller et al. [1] have quoted associations with many conventional cardiovascular risk factors which are consistent with their own findings, yet for almost every paper that describes an association with a given factor, there are several others which describe no such association. Although some of these paradoxes may be due to small data sets, even the large population-based studies differ in many of their findings, and there is very little convincing consensus in the literature [2–5]. The few areas in which consensus does exist include the association between smoking and sICAM-1 levels, which is again illustrated by Miller et al. [1], and the association between sICAM-1 levels and future cardiovascular risk in healthy populations [1–7]. This finding has been shared by all the large population-based studies to date, although meta-analysis suggests that it provides no additional predictive value above the assessment of conventional risk factors [3]. Miller et al. may establish whether this finding is independent of ethnicity by following their population.

Cellular adhesion molecules comprise several families of transmembrane glycoproteins and mediate cell–cell and cell–extracellular matrix interactions [8–10]. Some interactions are relatively static and contribute to the maintenance of the three-dimensional structural integrity of tissues, whereas others, such as those involved in the recruitment of leucocytes to sites of inflammation or developing atherosclerotic lesions, are transient over short periods of time. Cellular adhesion molecules may be shed from the cell surface into the plasma, and it is associations with plasma levels that have been explored in most clinical studies, including that by Miller et al. [1]. However, in mediating interactions between a cell and its environment, it is clear that the major biological function of most cellular adhesion molecules is at the cell surface. Little is known of the mechanism by which shedding occurs or by which molecules are cleared from the circulation after shedding, and the relationship between plasma levels and cell-surface activity is unclear and unpredictable [11]. Lower plasma levels could potentially reflect less shedding and therefore be associated with higher, rather than a perhaps more intuitive association with lower, cell-surface levels. Indeed, even the relationship between protein synthesis and cell-surface activity may not be easily predicted, since the latter is also influenced by the rate of shedding [12]. For example, statin exposure of endothelial cells in culture is associated with a decrease in protein synthesis for both VCAM-1 and E-selectin and, although there is the predicted decrease in cell-surface expression of VCAM-1, there is an apparently paradoxical increase in cell-surface expression of E-selectin, due to decreased shedding [12]. It is likely that issues such as these may explain some of the inconsistencies in the published data.

In the clinical setting, further apparent paradoxes are evident. For example, despite the laboratory findings above, statin therapy has been associated with no change in plasma levels of cellular adhesion molecules [13]. Additionally, although patients with hypertriglyceridaemia have been found to have higher levels of sICAM-1, sVCAM-1 and soluble E-selectin than normal control subjects, triacylglycerol (triglyceride) levels and adhesion molecule levels are not correlated, suggesting that other factors may be involved in directly influencing plasma levels [14]. Again, apparently paradoxically, elevated plasma levels of cellular adhesion molecules may be associated with decreased effective cell-surface activity and a decreased capacity to recruit leucocytes to a developing atherosclerotic lesion [14].

The examples above of apparent paradoxes in the data serve to illustrate the possible perils of simply equating plasma levels, or even cell-surface levels in isolation, with cell-surface activity and atherogenic potential. As Miller et al. [1] state, the results from one population cannot readily be extrapolated to other populations. In this regard, it should be remembered that, although Miller et al. [1] found lower plasma levels in one low-risk population, black subjects, they found no increase in levels in their high-risk population, South Asians.
Perhaps more importantly, however, as the authors [1] intimate, their findings suggest that genetic differences in either the activity or sensitivity of the adhesion molecule pathway between ethnic groups may exist. The pathophysiological consequences of any such differences, however, cannot be simply deduced from differences in plasma levels, as illustrated above. There may be differences in cell-surface levels or alternatively the differences may be only in plasma levels. Having raised the question of possible ethnic differences in the adhesion molecule pathway, the issue now merits further investigation at a more basic and fundamental level, by exploration of any differences between endothelial cells from subjects of different ethnicity, since understanding such potential differences may reveal new avenues amenable to future therapeutic exploitation.

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