Searching for new coronary heart disease risk factors

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The clinical consequences of atherosclerosis (e.g. stroke, myocardial infarction) are responsible for about one third of all deaths in the Western world. The physician’s ability to predict the development of a cardiovascular event in an individual patient is limited by the relatively low prognostic specificity of conventional risk factors for atherosclerosis. A search for more specific atherosclerotic risk factors is therefore justified in order to facilitate identification of individuals with a high risk of cardiovascular disease.

Microalbuminuria was originally associated with cardiovascular mortality in patients with Type 2 diabetes, but its independence from other risk factors was not clearly established[1,2]. In the late 1980s and early 1990s, two independent studies of limited sample size observed a high prevalence of cardiovascular disease among individuals with microalbuminuria in the general population. These two studies were also able to show that microalbuminuria was associated with an increased incidence of cardiovascular mortality in follow-up observations ranging from 4 to 8 years, thus establishing microalbuminuria not simply as a ‘risk factor’ of atherosclerotic disease but as a ‘predictor’ of cardiovascular disease events[3–5]. Following these seminal observations a number of other publications have confirmed the value of microalbuminuria as a predictor of cardiovascular disease morbidity and mortality in the general population, in Type 1 and Type 2 diabetes and possibly in essential hypertension[6]. The article by Diercks et al.[7] in this issue takes the quest for new atherosclerotic risk factors a step further by showing, in a large representative non-diabetic population of 7579 individuals, that microalbuminuria is associated with Minnesota coded electrocardiographic abnormalities of myocardial infarction (odds ratio; 95% CI: 1.61; 1.12–2.32) major ischaemia (1.43; 1.08–1.91) and minor ischaemia (1.32; 1.03–1.68) independent of other major risk factors including age above 60 years, male sex, hypertension, hypercholesterolaemia, smoking, obesity and family history of cardiovascular disease.

This observation agrees with recent reports from the Copenhagen City Heart Study[8] and the first MONICA (Monitoring trends and determinants in cardiovascular disease) Population Study[9] that microalbuminuria and an A/C ratio above the upper decile (i.e. ~0.65 mg . mmol⁻¹) of the normal distribution are significantly and independently associated with a relative risk of approximately 2.3 for development of ischaemic heart disease. Importantly these data also indicate a temporal relationship between elevated albumin excretion rate and subsequent cardiovascular disease events which was not confounded by the presence of previous clinically apparent ischaemic heart disease or diabetes.

Although the increase in urinary albumin excretion is consistently accompanied by an increased capillary leakage of albumin in the whole body[10], the reasons for the increased cardiovascular risk in subjects with microalbuminuria are largely unknown. In diabetes, microalbuminuria is associated with an adverse lipid profile[11] with evidence of generalized endothelial dysfunction[12] and with insulin resistance[13], the latter of which have been suggested as potential mediators of both raised urine albumin excretion and cardiovascular disease. Insulin resistance has been associated with microalbuminuria in diabetic subjects[13], their relatives and non-diabetic subjects[14], and has recently been related to inflammatory markers, such as C-reactive protein[15]. A strong relationship between C-reactive protein and the development of atherosclerotic disease has been observed in experimental and clinical studies[16]. Very recently, a significant association between C-reactive protein and fibrinogen on the one hand, and albumin excretion rate in the microalbuminuric range on the other, has been described in Type 2 diabetic as well as non-diabetic individuals[17], suggesting that chronic inflammation could be a possible mechanism linking microalbuminuria and macrovascular disease. In a report from the Hoorn Study[18], a large population study of cardiovascular risk factors in the Netherlands, microalbuminuria and pre-existing atherosclerotic disease independently predicted cardiovascular and all-cause mortality, indicating that microalbuminuria affects mortality risk through a mechanism distinct from generalized atherosclerosis. This finding, though at variance with that of the MONICA Study[9], is in accord with the results of a cohort study of Type 2 diabetes, in which microalbuminuria not only predicted incident coronary heart disease, but was, in turn, predicted, in patients with a normal baseline albumin excretion rate, by pre-existing coronary heart disease[19]. This suggested that microalbuminuria and atherosclerotic disease may not be causally related but rather reflect common determinants. It is possible therefore that, also in the general population, microalbuminuria, elevated levels of inflammatory proteins and atherosclerosis may
result from a common antecedent. An increased production of inflammatory cytokines such as IL-6 is a likely candidate, as recently suggested by studies in a mouse model of atherosclerosis.[20]

Beyond scientific and academic speculation there is, however, a very practical aspect to the intriguing association between microalbuminuria and ischaemic heart disease in the general population as well as in diabetes and hypertension. The detection of microalbuminuria is straightforward, easy and inexpensive to perform and may be used to identify subjects at increased cardiovascular disease risk and to prompt screening for other risk factors. It remains to be seen whether microalbuminuria is a modifying risk factor whose correction, as in the case of hypercholesterolaemia or arterial hypertension, would reduce, in its own right, the incidence of cardiovascular disease morbidity and mortality. Following on from this, the HOPE study[21] recently reported that the protection from cardiovascular disease events afforded by ramipril, a member of a class of drugs with specific antiproteinuric effects, seemed to be greater, though not significantly, in subjects with microalbuminuria compared with those with normoalbuminuria (risk reduction 29% vs 18%).

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References