How heterogeneous is microalbuminuria in diabetes mellitus? The case for ‘benign’ and ‘malignant’ microalbuminuria

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Introduction

The concept of microalbuminuria was introduced more than 30 years ago when it became possible to measure concentrations of urinary albumin below the level of detection of a urinary protein dipstick [1]. By the early 1980s, microalbuminuria had been shown to predict the development of nephropathy in insulin-dependent diabetic (IDDM) patients [2], leading to the view that the excretion of increased amounts of urinary albumin in these patients was an early manifestation of the pathophysiological process which, as a final consequence, led to renal failure.

Microalbuminuria also predicts dipstick-positive proteinuria and nephropathy in patients with non-insulin-dependent diabetes (NIDDM) [3], but in these patients its major prognostic significance is for increased cardiovascular risk [4]. More recent observations have extended the concept of microalbuminuria as a risk marker for cardiovascular disease to subjects without diabetes, in whom an elevated albumin excretion rate has been shown to predict a mortality up to 24 times that of normoalbuminuric subjects [5]. Furthermore, in IDDM patients, both dipstick-positive proteinuria [6] and microalbuminuria [7,8] are markers of cardiovascular risk. Various abnormalities of cardiovascular risk factors have been found in both diabetic and non-diabetic subjects with microalbuminuria, including hypertension, dyslipidaemia, procoagulant changes in clotting factors and insulin resistance [9], but even in combination these seem unlikely to explain the excess cardiovascular risk.

The common links of microalbuminuria and proteinuria to cardiovascular disease in subjects both with and without diabetes have led to the concept of a single disease entity. This view has been supported by several findings. In IDDM, nephropathy tends to cluster in families [10], and there is an increased prevalence of both hypertension [11] and coronary heart disease [12] among the non-diabetic parents of patients with nephropathy. With regard to NIDDM, it has been reported that non-diabetic relatives of NIDDM patients with microalbuminuria have an elevated albumin excretion rate [13]. These observations have been taken to imply that a common predisposition, possibly of genetic origin, may underlie both the familial clustering of microalbuminuria and its link to cardiovascular disease.

Recent studies, however, have suggested a substantial heterogeneity in the phenotypic characteristics of microalbuminuric diabetic patients. These findings raise the possibility of a more diverse aetiology of microalbuminuria, which in turn challenges current thinking about the nature of its link with cardiovascular disease. We propose that microalbuminuria in diabetes is heterogeneous with respect to clinical features and renal histology. We suggest that this heterogeneity has conceptual, prognostic and therapeutic implications, and so is of clinical importance.

Microalbuminuria—the evidence for phenotypical and histological heterogeneity

In both IDDM and NIDDM, microalbuminuria clusters with hypertension, severe retinopathy and atherosclerotic cardiovascular disease. Microalbuminuria is associated with dysfunction of the vascular endothelium, which may underlie this clustering [14–16]. Nevertheless, there is increasing evidence of heterogeneity among these relationships [14,15,17–20].

The EURODIAB IDDM Complications Study has investigated the associations of microalbuminuria with other clinical and biochemical characteristics in a Europe-wide study of >3000 IDDM patients [17,18]. The albumin excretion rate correlated significantly with both systolic blood pressure and the plasma concentra-
tion of von Willebrand factor, a marker of endothelial dysfunction, but only in subjects with photographic evidence of diabetic retinopathy. Around half of the patients with microalbuminuria had no clinical evidence of retinopathy, and in this group there was no association of increasing albumin excretion with either blood pressure or endothelial dysfunction.

In IDDM patients with dipstick-positive proteinuria, renal histology shows mesangial expansion. Increased glomerular basement membrane width and arteriolar hyalinosis [21]. In general, patients with microalbuminuria have similar but less extensive structural lesions [21,22], but their severity is quite wide, ranging from values observed in normoalbuminuric patients to those observed in patients with overt proteinuria [21–24]. This variability is in keeping with the observation that not all IDDM patients with microalbuminuria progress to overt proteinuria [20]. Renal structure in IDDM has not been investigated in relation to endothelial dysfunction, but the presence of retinopathy and hypertension (which, as noted above, are closely related to endothelial dysfunction [18]) was associated with an increase in both mesangial volume and basement membrane width which was independent of the albumin excretion rate [25].

In NIDDM, microalbuminuric patients have increased blood pressure and more severe retinopathy and endothelial dysfunction than do normoalbuminuric patients [15,26]. Again, however, there is important heterogeneity among these associations [14,15,19]; in addition, there is some evidence—although by no means undisputed—that both dipstick-positive proteinuria [27] and microalbuminuria [28] are morphologically heterogeneous. Parving and colleagues performed renal biopsies in 35 NIDDM patients with persistent albuminuria and found typical diabetic nephropathy in 77%, about two-thirds of whom had diabetic retinopathy, vs none among patients with non-diabetic renal histological abnormalities [27]. Fioretto and colleagues biopsied 34 microalbuminuric patients and found changes typical of diabetic nephropathy in only 30%, whereas 30% had normal or near-normal histology. The remaining 40% had tubulointerstitial abnormalities and (or) arteriolar hyalinosis and global glomerular sclerosis, but no or minimal diabetic glomerulopathy, a pattern of injury they termed ‘atypical’ [28]. Proliferative retinopathy was observed only among those microalbuminuric patients who had typical diabetic glomerulopathy [28]. Fioretto et al. have shown recently that endothelial dysfunction, as estimated by plasma von Willebrand factor concentration, was present only in those microalbuminuric patients who, on renal biopsy, had either typical diabetic glomerulopathy or atypical patterns of injury but not in those with (near-) normal histology [19].

Such different phenotypic patterns may imply heterogeneity of aetiology and prognosis. In fact, in a prospective study in NIDDM, Stehouwer et al. have shown that the presence of endothelial dysfunction, as estimated by elevated plasma levels of von Willebrand factor, modified the relationship between microalbuminuria and cardiovascular disease risk, in that microalbuminuria was associated with an increased risk of new cardiovascular events only when endothelial dysfunction was present [15]. Thus, both in IDDM and, perhaps even more so, in NIDDM, the interrelationships among microalbuminuria, endothelial dysfunction, renal histology and diabetic retinopathy are clearly heterogeneous.

Microalbuminuria in diabetes mellitus: a new classification with aetiological and prognostic implications

We speculate that microalbuminuria in diabetes may have at least two, and possibly three, different aetiologies. To begin with, there appears to be one aetiology that involves a close link with generalized endothelial damage, and one that does not. We hypothesize that only microalbuminuria with generalized endothelial damage confers an increased risk of cardiovascular disease and renal failure. In other words, we postulate that microalbuminuria may be ‘benign’ or ‘malignant’. In addition, the recent findings on the interrelationships between endothelial dysfunction, renal histology and severity of diabetic retinopathy in NIDDM [14,19,28] raise the possibility of two subcategories of ‘malignant’ microalbuminuria in diabetes: one involving glycaemic and the other non-glycaemic pathways of vascular and endothelial injury. The fact that endothelial dysfunction is related to the atypical pattern of renal injury in NIDDM [14,19,28] may then be explained by postulating that this process does have a vascular aetiology, but one that depends less (or perhaps not at all) on hyperglycaemia than does typical diabetic glomerulopathy. This would also explain the occurrence of less severe diabetic retinopathy in the group with atypical renal histology than in those with typical diabetic glomerulopathy [28], because this latter group would have more severe specifically diabetic microvascular disease (of which proliferative diabetic retinopathy is a marker), while vascular damage in the former group would tend to be of both glycaemic and non-glycaemic origin. The prognostic implications of these hypotheses are summarized in Table 1.

A more precise phenotypic characterization of microalbuminuric subjects is necessary to assess the role of genetic and environmental determinants of the diverse types of microalbuminuria proposed above. For example, early growth retardation, abnormalities of sodium membrane transport, increased production of vascular endothelial growth factor, or polymorphisms in the constitutive nitric oxide synthase gene could predispose to the types of microalbuminuria that are associated with endothelial dysfunction, while polymorphisms in genes controlling the activity of intra-renal haemodynamics might lead to glomerular hypertension and microalbuminuria but not necessarily to generalized endothelial dysfunction. We further speculate that, in contrast to the other categories shown in Table 1, the category characterized by
Table 1. Prognostic implications of heterogeneity of microalbuminuria in diabetes mellitus

<table>
<thead>
<tr>
<th>Microalbuminuria in diabetes mellitus</th>
<th>Without generalized endothelial dysfunction ('benign')</th>
</tr>
</thead>
<tbody>
<tr>
<td>With generalized endothelial dysfunction ('malignant')</td>
<td>Typical/atypical renal histology*</td>
</tr>
<tr>
<td><strong>Risk</strong> of:</td>
<td>No increase</td>
</tr>
<tr>
<td>severe retinopathy</td>
<td>++ + / +</td>
</tr>
<tr>
<td>renal failure</td>
<td>++ + / + to + +</td>
</tr>
<tr>
<td>cardiovascular disease</td>
<td>++ + / + +</td>
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</tbody>
</table>

*As defined in the text; †As compared with subjects with normoalbuminuria.

microalbuminuria, endothelial dysfunction, typical diabetic glomerulopathy and severe retinopathy has its pathophysiological basis in biochemical alterations specifically linked to hyperglycaemia, such as hyperglycaemic pseudohypoxia, protein kinase C activation and advanced glycation end-product formation.

This new classification of microalbuminuria proposed here emphasizes that we need to address the nature of the link between microalbuminuria and endothelial dysfunction. For example, endothelial dysfunction might directly cause microalbuminuria both by contributing to the synthesis of a leaky glomerular basement membrane and by influencing glomerular mesangial and epithelial cell function in a paracrine fashion. Alternatively, both generalized endothelial dysfunction and microalbuminuria might develop in parallel as a result of some common underlying pathophysiological process, for which there is no lack of contenders but no definite proof [29].

Finally, a hypothesis of aetiological diversity in microalbuminuria could lead to differences in the therapeutic approaches indicated in such subjects. Microalbuminuric patients with endothelial dysfunction may merit especially intensive efforts with respect to the treatment of conventional cardiovascular risk factors. Moreover, a better understanding of the nature of endothelial dysfunction in diabetes might lead to more specific therapies, such as with free radical scavengers or glycosaminoglycans. While such consequences of heterogeneity of microalbuminuria are as yet speculative, each of them is amenable to epidemiological, clinical or experimental verification. For example, an important test of our hypothesis is to investigate whether treatments such as those with free radical scavengers do or do not improve endothelial function and microalbuminuria in parallel. If ‘benign microalbuminuria’ does exist, we would expect some microalbuminuric patients to have normal endothelial function and no reaction to such treatment.

**Microalbuminuria and cardiovascular disease in non-diabetic subjects: quo vadis?**

Microalbuminuria is a powerful risk marker for cardiovascular disease even in apparently healthy middle-aged and elderly subjects [5]. Therefore, both the occurrence of microalbuminuria and the link between microalbuminuria and cardiovascular disease do not necessarily require the presence of diabetes, i.e. they can occur through a diabetic or a non-diabetic pathway. We hypothesized above that the diabetic pathway involves damage to the vascular endothelium. Only a few small cross-sectional studies have addressed the question of whether a similar mechanism operates among non-diabetic subjects, with inconclusive results [30–32]. Moreover, other mechanisms unrelated to endothelial dysfunction need to be considered, such as a primary increase in vascular permeability [31,33] and matrix composition, and functional abnormalities in vascular smooth muscle cells, monocytes–macrophages or renal mesangial cells. Thus, data are as yet insufficient to support the idea that microalbuminuria and its link with cardiovascular disease have similar origins in diabetic and non-diabetic subjects. It is also unknown whether microalbuminuria in non-diabetic subjects may be prognostically heterogeneous (‘benign’ or ‘malignant’). In comparison with diabetes, microalbuminuria in non-diabetic subjects has as yet been poorly characterized both phenotypically and histologically.

**Conclusion**

We propose that microalbuminuria in diabetes mellitus is heterogeneous: benign and malignant. It may be associated with generalized endothelial dysfunction, severe diabetic retinopathy and cardiovascular disease, or it may lack such associations. This classification, if correct, has important prognostic, aetiological and possibly therapeutic implications. We emphasize, however, that our hypothesis at present is no more than an agenda for further research that has yet to be tested vigorously. In clinical practice, the presence of microalbuminuria should be regarded as a powerful indicator of an increased risk of renal failure and cardiovascular disease [34].

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