SUMMARY - Microalbuminuria was originally considered to be an important new risk factor for diabetic nephropathy. More recently, it has been convincingly shown that microalbuminuria is also an independent risk factor for cardiovascular morbidity and mortality in Type 1 and Type 2 diabetic patients. Even in the non-diabetic background population, microalbuminuria is a risk factor for cardiovascular mortality. What is the link between increased loss of albumin in urine and cardiovascular disease and mortality? As microalbuminuria is apparently associated with increased universal vascular sieving of albumin in terms of the transcapillary escape rate of albumin (TER-alb), microalbuminuria may reflect this universal sieving. The pathophysiology of increased TER-alb is unknown, but could be caused by haemodynamics or damage to the functional properties of the vascular wall. A number of studies have provided evidence of endothelial dysfunction in patients with microalbuminuria, which may be the common link accounting for the associations mentioned above. In this context, a number of markers of endothelial cell dysfunction have been found to be increased in patients with microalbuminuria. In addition, a number of functional in vivo tests of endothelial dysfunction have been performed in Type 1 and Type 2 diabetic patients as well as in normal controls. Overall, these studies indicate the existence of a functional vascular dysfunction in Type 1 diabetic patients and normal controls with microalbuminuria, which may be related to dysfunc-
tion of endothelial cells.

Key-words: diabetes, microalbuminuria, endothelium, cardiovascular mortality, flow-mediated vasodilatation.

RÉSUMÉ - Microalbuminurie, dysfonction endothéliale et risque cardiovasculaire.

Initialement, la microalbuminurie a été considérée comme un nouvel impor-
tant facteur de risque de néphropathie diabétique. Récemment, il a été démontré que la microalbuminurie est aussi un facteur de risque indépendant de morbidité et mortalité cardiovasculaires des diabètes de type 1 et de type 2. Même chez les sujets non diabétiques, la microalbu-
murie est un facteur de risque cardiovasculaire. Quel est le lien entre l’augmentation de l’albuminurie et le risque cardiovasculaire? La mi-
croalbuminurie étant associée à une fuite généralisée transcapillaire

d’albumine (FT-alb), nous avons posé l’hypothèse que la microalbuminu-
rie reflète cette FT-alb généralisée. La physiopathogénie de l’augmenta-
tion de FT-alb est inconnue. Elle pourrait résulter d’anomalies des pro-
priétés fonctionnelles de la barrière vasculaire. De nombreuses études

revèlent une dysfonction endothéliale chez des patients présentant une
microalbuminurie. Ceci pourrait représenter le lien expliquant les asso-
ciations évoquées ci-dessus. Plusieurs marqueurs de dysfonction des
cellules endothéliales ont été révélés chez des patients présentant une
microalbuminurie. De plus, des tests fonctionnels de dysfonction endo-
théliale ont été réalisés in vivo chez des diabétiques de type 1 ou type 2. Globalement, ces tests révèlent une dysfonction fonctionnelle vasculaire
chez les diabétiques de type 1 et chez les sujets témoins microalbuminu-
rices, et que ceci pourrait être lié à une dysfonction des cellules endo-
théliales.

Mots-clés: microalbuminurie, facteur de risque, cardiovasculaire, cel-
lule endothéliale, dysfonction, néphropathie.
Diabetic nephropathy is defined by proteinuria above 0.5 g/24 h. At this stage, kidney function is usually normal, but has in fact begun to decline towards end-stage renal failure. Blood pressure may be only slightly elevated, but has actually started a rapid increase towards severe hypertension. If this condition goes untreated, kidney function will be reduced on average by 10 ml/min/year, and median survival without renal support therapy will be 7 years. It has been known for some time that antihypertensive treatment in these patients is very important and can reduce the rate of decline in the glomerular filtration rate (GFR) to about 3-5 ml/min/year, which is of great clinical importance. In the early 1980s, it was shown that proteinuria, apart from defining diabetic nephropathy, is also associated with other late diabetic complications. Of even greater importance, it was determined that almost all of the excess mortality seen in Type 1 diabetic patients occurs among those who have developed proteinuria [1]. Only a small part of this excess mortality is attributable to death from end-stage renal disease. Most patients actually die from cardiovascular disease long before clinically important reductions in kidney function occur [2]. Therefore, an important question arises: What is the link between protein loss in urine and cardiovascular morbidity and mortality?

**Microalbuminuria**

In the late 1970s, new methods were developed for the detection of proteins in urine. With immunoassays, albumin could even be detected in normals. A total protein excretion of 0.5 g/day was shown to correspond to a urinary albumin excretion rate (UAER) of 300 mg/24 h, which became the new indicator of initial clinical diabetic nephropathy. As normal controls excrete albumin at a rate below 30 mg/24 h, which became the new indicator of baseline values for the UAER, response to exercise was quite marked [7], indicating that a change had occurred in the filtering barrier in patients with microalbuminuria. It was then considered that this change in the glomeruli might in fact be present throughout the vascular bed.

**Microalbuminuria and Cardiovascular Disease**

In the past decade, a number of studies have clearly demonstrated that microalbuminuria is not only a risk factor for diabetic nephropathy, but also an independent risk factor for cardiovascular mortality in Type 1 diabetes, Type 2 diabetes and apparently healthy controls [8-11]. These observations have raised the question as to whether urinary albumin is an indicator of cardiovascular morbidity and mortality.

**Microalbuminuria and Universal Vascular Sieving**

It has been shown that the transcapillary escape rate of albumin is significantly elevated in subjects with microalbuminuria. This is the case for Type 1 diabetic patients and healthy controls [12, 13]. Moreover, the transcapillary escape rate is elevated in patients with severe atherosclerosis, who also have microalbuminuria [14]. This rate is an indication of the amount of albumin leaving the vascular bed per hour. In normal controls, about 5% per hour leaves the vascular bed (and returns, of course, through lymphatic vessels in the following hours). Therefore, an increase in TER-alb and microalbuminuria is indicative of universal vascular leakage, which should be present in patients as well as healthy controls with microalbuminuria [15]. If this is the case, the link between cardiovascular disease and microalbuminuria may relate to certain changes that take place in the entire vascular bed, including the kidneys. In these early stages of microalbuminuria, excess loss in urine may not reflect kidney disease but rather a universal vascular leakage, which could be the link between cardiovascular disease and microalbuminuria.

**Endothelial Dysfunction**

A large number of mechanisms could be responsible for such alterations in universal vascular leakage. As the endothelium plays a very central role in vascular function, it is tempting to speculate that endothelial dysfunction is the primary event. If this were the case, very small increases in UAER could reflect such a universal dysfunction both in apparently healthy subjects and in diabetic patients (who in the following years would develop clinical signs of cardiovascular disease). In vivo studies of endothelial dysfunction, though numerous, suggest no very definite conclusions at the present time. A number of markers in plasma reflect endothelial cell function (or dysfunction), including von Willebrand factor [16], angiotensin-converting enzyme (ACE) [17], adhesion molecules sVCAM1 and sICAM1 and e-selectin [18-23]. Endothelin should also be included in this list.
Elevated levels of von Willebrand factor have been found in Type 1 and Type 2 diabetic patients, particularly in Type 1 patients with microalbuminuria, and increases in von Willebrand factor are considered to be predictive of progression to microalbuminuria in healthy controls [24]. High ACE levels have also been reported in Type 1 patients with microalbuminuria. Adhesion molecules were found to be elevated in Type 1 and Type 2 patients, particularly in Type 1 patients with microalbuminuria. Although there is no conclusive evidence, these observations all suggest that endothelial cell dysfunction occurs in diabetic patients and healthy controls with microalbuminuria.

A functional test of endothelial cells can be performed by various techniques, e.g. forearm blood flow using plethysmography, vasodilation in the forearm skin, or flow-mediated vasodilation. All these tests show that there is evidence of endothelial cell dysfunction in both Type 1 and Type 2 patients [19-22]. The effect of glycemic control and microalbuminuria on blood pressure has not yet been firmly established. In apparently healthy controls with an elevated UAER, flow-mediated vasodilation is significantly altered as compared to normoalbuminuric healthy controls.

All of these observations suggest, but do not prove, that endothelial dysfunction is the initial event in the development of microalbuminuria.

A large number of animal studies, which will not be reviewed here, have demonstrated that advanced glycation end-products and hyperglycaemia, at the diabetic stage per se, can affect the interaction between endothelial cells and smooth muscle cells in various models.

CONCLUSION

Microalbuminuria is not only a risk factor for diabetic nephropathy but also an important independent risk factor for cardiovascular morbidity and mortality in Type 1 and Type 2 diabetic patients as well as in apparently healthy controls. A relation has been established between increased loss of albumin in urine and universally increased sieving of albumin from the entire vascular bed. In this context, many studies indicate that endothelial cell dysfunction may be the initial common link between microalbuminuria and cardiovascular morbidity and mortality.

REFERENCES

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