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Microalbuminuria and Cardiovascular Complications:
Is microalbuminuria the best marker for endothelial dysfunction?

Adapted from a lecture by: DR. NORMAN K. HOLLENBERG, Professor of Medicine, Harvard Medical School

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Introduction

How does one predict the risk of cardiovascular complications in patients with diabetes mellitus or hypertension? Cardiologists have for a long time focused on standard risk factors for the development of vascular disease, for example smoking status, serum cholesterol, the extent of blood pressure elevation, and others. Although these factors are clearly related to an increased risk for developing cardiovascular complications, they are only modestly useful in predicting the risk in individual patients. It is being increasingly understood that it is difficult to monitor the tissue and vascular complications of diabetes and hypertension, for example myocardial infarction, stroke, or left ventricular hypertrophy, until it is too late or almost too late. In an important review of the information clinicians can obtain from examining renal function in diabetic and hypertensive patients, Dr. Hollenberg discussed the pathogenesis, detection, and clinical implications of microalbuminuria at a recent symposium allied to the Canadian Cardiovascular Society 1996 Annual Meeting.

What is microalbuminuria?

In normal individuals, there is a small amount of albumin excreted in the urine, ranging from 1-22 mg per day, and varying with posture, exercise, and blood pressure. When the daily urinary albumin excretion ranges from 30-300 mg, microalbuminuria is present, with frank proteinuria at levels >300 mg/day. Microalbuminuria is common in patients with illnesses predisposing to cardiovascular events, occurring in 20-25% of type II diabetic patients and 25% of treated hypertensives and up to 40%

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of untreated hypertensive patients.[1] Microalbuminuria is caused by glomerular damage, and altered intrarenal hemodynamics, which result in increased glomerular filtration of albumin, increased intraglomerular pressure, as well as glomerular endothelial dysfunction. In diabetics, although this is not clearly known for hypertensive patients, there are also changes in capillary barrier charge-selectivity in the glomerulus. The excess albumin presented to the proximal renal tubule cannot be reabsorbed. Microalbuminuria may represent the renal manifestation of a generalized, genetically conditioned vascular endothelial dysfunction, which may provide the link between increased urinary albumin excretion and an elevated risk for cardiovascular events.[2,3] Although the pathogenesis of the renal disorder (glomerulosclerosis) in diabetes and hypertension is not entirely clear, a high renin activity in renal tissues is thought at least in part to be responsible, despite the fact that in diabetes, for example, plasma renin values tend to be low. However, the local activation of tissue angiotensin receptors leads to a molecular cascade resulting in the activation of multiple protein kinases, which in turn lead to tissue proliferation. These general mechanisms may be similar in the heart, where they may cause myocardial remodeling, and left ventricular hypertrophy; in blood vessel walls where they may cause endothelial and medial changes in coronary arteries; and in the kidney where they cause glomerulosclerosis.

How can microalbuminuria be detected?

Since urinary albumin excretion is common but highly variable, routine "dipstick" measurements can generally be used for screening of microalbuminuria. However, the best test is agreed to be the albumin/creatinine ratio in an early morning urine sample (abnormal is >30 mg/gram of creatinine) or as an excretion rate, in an overnight urine collection, of >20 micrograms of albumin per minute. These screening tests are simple, little affected by exercise, and show only moderate intra-individual variation.

What are the clinical correlates of microalbuminuria?

Microalbuminuria is the crucial marker for the risk of developing frank nephropathy in patients with diabetes and hypertension. In insulin dependent diabetes, the presence of microalbuminuria almost invariably implies the subsequent development of frank proteinuria and ultimately serious nephropathy, with an increase in albuminuria of 10-30% per year, correlating with poor glycemic control or blood pressure elevation. In non-insulin dependent diabetes patients, the average increase in albuminuria is about 15-20% per year.[4] This progression to overt proteinuria and the risk of end stage renal failure can be forestalled or reversed with effective therapy. Once frank albuminuria (>300 mg/day) is present, glomerular filtration rate declines progressively to complete renal failure within 7-10 years.[4]

Importantly, microalbuminuria is highly correlated with the risk of developing non-renal, vascular complications of diabetes and hypertension. In patients with 25 years or more of diabetes and nephropathy, cardiovascular mortality is 10 times higher than in comparable diabetics without nephropathy, and 50 times higher than in

the general population.[5] Patients with diabetes or hypertension frequently have other cardiovascular risk factors such as hyperlipidemia, hypertension, and coagulation abnormalities. However, microalbuminuria appears to confer an independent risk for the development of premature vascular disease, and this has been hypothesized to be due to the simultaneous development of similar structural defects within the glomeruli in the wall of medium and large-sized arteries, such as the coronary arteries.[6]

In view of the simplicity of its measurement, and the fact that it can be detected before the clinical appearance of other forms of vascular disease (angina, transient ischemic attacks, claudication, etc.), screening for microalbuminuria seems an ideal test for the early detection of the propensity to serious vascular complications of diabetes and hypertension (Table 1 – adapted from Hollenberg, K.).

The Scientific Advisory Board of the National Kidney Foundation have recommended screening for albumin excretion in all diabetic patients at least once per year, and although similar recommendations have not yet been made for patients with hypertension, this is likely to be a reasonable and cost effective screening strategy. The World Health Organization criteria for justification of mass screening for diseases include presence of an important health problem, sufficient knowledge of the natural history of the disease, the availability of effective treatment, the existence of risk groups, the availability of simple screening tests, and advantageous cost/benefit ratio. These factors are definitely present for diabetes and probably present for hypertension with respect to microalbuminuria and vascular complications.

How should one treat microalbuminuria?

In diabetics, there is almost universal consensus that the drug treatment of first choice should be ACE inhibition, which is effective in preventing the progression for microalbuminuria to overt nephropathy.[7] ACE inhibitors are more effective than beta blockers or calcium antago-

Microalbuminuria and Target Organ Damage

It predicts	**Diabetes Mellitus**	**Essential Hypertension**
All cause mortality	Yes	Yes
Fatal CVD	Yes	Yes
Non-fatal CVD	Yes	Yes
Nephropathy	Yes	Unknown
It is associated with:	**Diabetes Mellitus**	**Essential Hypertension**
LVH	Yes	Yes
Insulin-resistance/hyperinsulinemia	Yes	Yes
Dyslipidemia	Yes	Yes
Retinopathy	Yes	Yes
PVD	Yes	Unknown
Peripheral and autonomic neuropathy	Yes	Unknown

nists in diminishing albuminuria, and they do so at lower levels of blood pressure reduction than other antihypertensives. In addition to glycemic control in diabetics, the administration of ACE inhibitors has been shown to significantly reduce urinary albumin excretion rate. Initial studies were conducted with captopril and enalapril, and more recent studies with other ACE inhibitors have shown similar results.[7]

In a recent study of hypertensive patients with type II diabetes, Corradi et al[8] showed a significantly greater and more rapid reduction in microalbuminuria following the use of the ACE inhibitor fosinopril than the calcium antagonist amlopidine, despite similar levels of blood pressure reduction. In another study comparing fosinopril and amlodipine in previously untreated hypertensive patients, only fosinopril significantly decreased microalbuminuria.[9]

What are the implications for cardiologists?

Whether the underlying pathophysiology in coronary and peripheral blood vessels and renal blood vessels is the same or not, renal vascular (endothelial) dysfunction resulting in microalbuminuria is highly correlated with the propensity to vascular complications. As such, it is a simple, efficient, and easily applied tool for screening patients with diabetes and probably hypertension. In patients with significant microalbuminuria, all possible attempts should be made to alter reversible risk factors such as smoking, hypertension, hyperlipidemia, and obesity. ACE inhibitors are clearly beneficial in reducing the risk of progressive renal dysfunction. They are also clearly of benefit in the secondary prophylaxis of recurrent cardiovascular events in patients with left ventricular dysfunction, left ventricular failure, and recent myocardial infarction. Whether they will be beneficial in the primary prevention of vascular events in patients at risk is not clear, but treatment with ACE inhibitors appears reasonable in view of the emerging evidence for their efficacy as "vasculoprotective" agents.

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