MICROALBUMINURIA IN TYPE-1 DIABETES MELLITUS

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Introduction

The prevalence of Type-1 diabetes had increased in most European populations and it may also be rising among US youth (1). The prevalence, incidence and mortality of end-stage renal disease (ESRD) (2) and from all forms of cardio-vascular disease (CVD) (3) are strikingly increased in persons with diabetes compared to those without diabetes. In all likelihood, an earlier onset of diabetes will lead to an earlier onset of CVD complications. Importantly, recent non-invasive studies in youth with Type 1 diabetes show early increases in coronary calcification and elevated CVD risk factors (1). The presence of diabetic nephropathy, that appears many years before the development of clinically relevant cardiac and arterial damage, further increases the risk for CVD diseases. Indeed, one of the major goals is to prevent development of diabetic nephropathy.

Recent studies have now demonstrated that the onset and course of diabetic nephropathy can be ameliorated to a very significant degree by several interventions, but these interventions have their greatest impact if instituted at a point very early in the course of the development of this complication. Microalbuminuria, i.e. small amounts of urinary albumin excretion (UAE), is the best predictor of high risk of developing diabetic nephropathy (4). Thus, the detection of microalbuminuria has played a key-role in the management of type-1 diabetes.

Assessment and clinical value of microalbuminuria

Microalbuminuria is defined as the appearance of low but abnormal levels of albumin in the urine (30-300mg/24-hour; 20-200 mcg/min; 30-300 mg/g creatinine). In microalbuminuric patients not receiving antihypertensive treatment, 80% progress to an increase in UAE rate of 6% to 14% per year and a risk for developing diabetic nephropathy of 3% to 30% per year. Microalbuminuria rarely occurs shortly after patient develops type-1 diabetes. Therefore, screening in these individuals should begin after 5 years of disease duration. A sensitive method, the Micral test, radioimmunoassay or enzymoimmunoassay, for albumin should be used and repeated every year if the result is negative. If the result is positive, microalbuminuria can be confirmed and quantified by measuring the ratio of albumin to creatinine in a morning urine sample or by measuring the rate of albumin excretion in a 24-hour or overnight urine sample. Overnight samples can be used to distinguish true microalbuminuria from postural or exercise proteinuria, which are common in young patients. Since short-term hyperglycemia, exercise, urinary tract infection and acute febrile illness can cause transient elevations in UAE, and there is also marked day-to-day variability in UAE, at least two of three collections done over a 3-6 month period should show elevated levels before designating a patient as having microalbuminuria. Isolated microalbuminuria usually indicates the presence of early diabetic nephropathy, but the presence of other abnormalities upon urinalysis may suggest another renal disease (5).

Significance of microalbuminuria

The relationship between microalbuminuria and renal functional and structural abnormalities has been analyzed. Glomerular hyperfiltration, increments in renal plasma flow and nephromegaly have been recognized for many years in Type-1 diabetes, and an enhanced risk to develop microalbuminuria has been proposed in these patients. A clear relationship between hyperfiltration and microalbuminuria, however, has not been demonstrated (6). Likewise, structural abnormalities correlate poorly with isolated microalbuminuria. Mauer et al. (7) observed that in patients with microalbuminuria in the lower range and otherwise normal glomerular filtration rate (GFR) and BP, the mesangial volume fractions completely overlapped with those in patients whose renal function was normal. In contrast, patients with microalbuminuria and either hypertension, decreased GFR or both had more advanced mesangial expansion.

Whether or not microalbuminuria indicates the presence of more generalized structural or functional abnormalities outside of the kidneys has been analyzed. Endothelial dysfunction, estimated for a reduction in the vasodilatory capacity to reactive ischemia or to acetylcholine infusion in isolate arm, or for an impairment of insulin-mediated skeletal muscle blood flow, has been demonstrated. Furthermore, microalbuminuria has been associated with incipient neuropathy, proliferative diabetic retinopathy, and coronary heart disease (8).

Risk factors for microalbuminuria

Identification of factors related to the development of microalbuminuria leads to the development of strategies to reduce the occurrence of new cases. Several main factors have been identified. Among them, metabolic control, blood pressure levels and genetic factors are the most studied.

A large body of evidence implicates poor *metabolic control* with the risk of developing microalbuminuria. Elevated levels of glucose increase the risk, not only for the short term, through the generation of advanced glycated proteins, activating an isoform of the protein kinase C and increasing the sensitivity to angiotensin II. What is controversial is whether or not there is a glycemic threshold for risk. Data coming from cross-sectional, follow-up and intervention studies has not supported the existence of a threshold, and efforts to reduce HbA1c should, therefore, be continued at all levels (9).

Several studies have reported that *systemic blood pressure* is not raised prior to the onset of microalbuminuria. Using ambulatory blood pressure monitoring, however, it has become evident that in Type 1 diabetics with microalbuminuria, nocturnal blood pressure is already higher than in Type 1 diabetics with normoalbuminuria or in age matched control subjects (10). Consequently, these studies have shown that in Type 1 diabetics the presence of microalbuminuria is often associated with subtle alterations in blood pressure, characterized by a "non-dipping status" (11). The relationship between nighttime BP and urinary albumin excretion has been previously documented, and the BP parameter which best correlated with urinary albumin excretion was nighttime BP. High BP during sleep leads to renal damage due to the transmission of systemic BP into glomerular and tubulointerstitial structures and is facilitated by the low preglomerular tone during recumbence and resting conditions that is more marked in diabetic subjects than in normal subjects. Whereas, there is the potential role for systemic BP transmission to act as a renal damage-inducing mechanism, other evidence supports the thesis that higher sleep BP may be a consequence of the incipient renal damage itself.

leading consequently, to higher sleep BP. Neither the cause nor the consequence interpretation of these data is mutually exclusive. The impact of lowering nocturnal BP on reducing the development of nephropathy and/or cardiovascular damage remains to be confirmed in the future.

Familial clustering of diabetic nephropathy suggests the presence of *genetically transmissible factors* that modulate the risk of nephropathy. The Insertion/Deletion of angiotensin converting enzyme (ACE) gene has been one of the first and is the most studied gene due to the influence of the polymorphism in the activity of ACE, a key enzyme in angiotensin II generation. Several studies have demonstrated that the D allele is an independent risk factor in facilitating the onset of diabetic nephropathy [12]. Association with the polymorphism of other candidate genes is less consistent.

Other factors frequently associated with the development of microalbuminuria risk are smoking, obesity and dyslipidemia. The impact of each of these, and their interaction with the three main factors is difficult to assess, but if any of it are present, they should be taken into account in the management of these patients.

Treatment of microalbuminuria

Glycemic control is the first goal to be achieved in diabetic subjects [13]. Although randomized studies comparing the renal effect of intensified blood glucose control to conventional treatment did not demonstrate significant differences, long term intensified therapy in the Diabetes Control and Complications Trial (DCCT) [14] reduced the risk of proteinuria by 54%. Achieving HbA1c < 7% is a reasonable target

Based on well-conducted clinical trials, angiotensin-converting enzyme inhibitors (ACEi) are recommended for all patients with Type 1 diabetes and microalbuminuria, regardless of BP values [15]. In a recent meta-analysis based in 698 individual data from studies which had a placebo or a nonintervention group and at least 1 year of follow-up, patients receiving ACEi prevent progression of albumin excretion rate from the microalbuminuric to the clinically proteinuric range and can normalize albumin excretion rate in patients with microalbuminuria [16], indicating that ACEi may help to reverse renal disease. The effect of ACEi does not differ by sex, age, disease duration, glycemic control and baseline blood pressure, but the effect seems to be partially independent of the BP lowering effect.

Experience with angiotensin receptor blockers (ARBs) is scarce. Although a significant reduction in UAE with losartan has been observed, one similar to that those observed with enalapril, no evidence exists in terms of advantages over ACEi. Thus, ACEi is still the recommended drug in these patients, unless ACEi intolerance exists.

Prevention

There are two main strategies that have been evaluated to avoid the progression from normoalbuminuria to microalbuminuria, the improvement of glycemic control, and the administration of blood pressure lowering agents [17]. Concerning the impact of improving glycemic control, Wang and coworkers published a meta-analysis of 12 studies comparing the effect of intensive versus conventional blood glucose control on the risk of progression to nephropathy in patients with normoalbuminuria and microalbuminuria. The risk defined as an increment in UAE was decreased with the intensified treatment, odds ratio of 0.34 [18]. Likewise, in the DCCT intensified therapy reduced the occurrence of microalbuminuria by 39%, but the effect does not occur for at least three years.

ACEi also significantly reduces the albumin excretion rate below the threshold to define microalbuminuria even in patients with relatively little albumin excretion rate. Although the magnitude of the effect in such patients is not as great as in those with higher rates, it is nonetheless of statistical and probably clinical significance. The EUCLID study, a randomized placebo control trial, demonstrates that lisinopril is able to reduce the occurrence rate of microalbuminuria by 30% [19]. Indeed, ACEi may also be used in treating normoalbuminuric subjects at high risk of develop an increase in the urinary albumin excretion rate.

It is still likely that progression to microalbuminuria will occur in a substantial proportion of patients, and therefore there is a need to explore the role of risk factors other than glycemic control, reducing BP or decreasing angiotensin II activity that may provide further clues for interventions. Looking for early markers of risk can help a selective and prompt therapy to protect the patient from the development of microalbuminuria and the likelihood of diabetic nephropathy. Until these markers can be identified, detection of UAE in the high normal range needs to be considered for early intervention due to the risk of progression and because it is now clear that the significance of microalbuminuria extends beyond nephropathy. It is also a marker for generalized vascular dysfunction and cardiovascular risk in the diabetic population.

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