Commentary: Microalbuminuria: Past, present and glorious future

Hans-Henrik Parving

Department of Medical Endocrinology, Rigshospitalet, University of Copenhagen, Blegdamsvej 7-9 DK-2100 København Ø DENMARK. E-mail: hhparving@dadlnet.dk

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In 1969, Keen and colleagues demonstrated increased urinary albumin excretion (microalbuminuria) during a 50-g glucose load in people with diabetes, compared with those with borderline diabetes and controls, applying a sensitive radioimmunoassay method. The 2-h urinary albumin concentration correlated positively with blood glucose and blood pressure in the diabetic group. This led the authors to suggest: ‘The therapeutic implications of this is that treatment of hypertension associated with diabetes may ameliorate or delay the onset of renal disease’.

Increased urinary albumin excretion is the net result of glomerular capillary passage and tubular reabsorption. Increased glomerular albumin passage occurs due to functional and structural abnormalities such as: increased glomerular capillary permeability-surface area product (size and charge selectivity); and elevated glomerular hydraulic pressure. Recently, the importance of the glycocalyx for macromolecular transvascular transport has been documented. Poor glycemic regulation and diabetes reduce the glycocalyx, leading to increased albuminuria. Studies in diabetic animals and man have demonstrated enhanced size and charge selectivity for large macromolecules and raised measured and estimated glomerular capillary hydraulic pressure.

The landmark study by Keen et al. created an avalanche of retro- and prospective observational studies demonstrating the predictive power of microalbuminuria for: diabetic nephropathy, end-stage renal disease, fatal and nonfatal cardiovascular events in type 1 and type 2 diabetes, hypertension and in the general population.

The mechanisms linking microalbuminuria with fatal and nonfatal cardiovascular disease remain poorly understood. Microalbuminuria has been proposed as a marker of widespread endothelial dysfunction that might predispose to enhanced penetrations in the arterial wall of atherogenic lipoprotein particles (the Steno hypothesis). Secondly, microalbuminuria has been suggested simply as a marker of established cardiovascular disease. Thirdly, microalbuminuria is associated with excess of well-known cardiovascular risk factors such as: elevated blood pressure, dyslipoproteinaemia, increased platelet aggregability, insulin resistance and autonomic neuropathy.

It is important to recall that no therapy was available for preventing or treating overt diabetic nephropathy in 1969. My own experience between 1975 and 1980 as a senior registrar at Steno Diabetes Center in Copenhagen, caring for approximately 6000 diabetic patients, can be described as a hospital flooded with young type 1 diabetic patients with end-stage renal disease, waiting to die. No therapy was available, including dialysis/transplantation which were not offered by our nephrologists because our patients frequently suffered from several severe vascular and neurological complications.

Two to three decades later, numerous studies have demonstrated a renoprotective effect of improved glycemic regulation, arterial blood pressure reduction, blockade of the renin-angiotensin system independent of blood pressure and intensified multifactorial intervention—with tight glucose regulation, and the use of renin-angiotensin system blockers, aspirin and lipid-lowering agents.

Glycemic regulation has mainly a beneficial effect early in the development of diabetic nephropathy i.e. progression from normoalbuminuria to microalbuminuria. Blood pressure reduction, blockade of the renin-angiotensin system and intensified multifactorial intervention act on every stage of development and progression of diabetic nephropathy and end-stage renal disease. It should also be stressed that the above-mentioned treatment modalities can induce regression of urinary albumin excretion rate, and thereby preserve measured glomerular filtration rate. Those studies suggest that microalbuminuria is a risk factor for diabetic nephropathy [end-stage renal disease (ESRD)].

Recently many new biomarkers have been evaluated as predictors for renal risk in diabetic patients, but apart from urinary proteomics (expensive, time-consuming and with limited access), none has yet
outperformed Harry Keen’s discovery of microalbuminuria as the best screening tool for diabetic kidney disease. Microalbuminuria has also stood the test of time as a valid powerful independent predictor for fatal and nonfatal cardiovascular outcomes in diabetes.

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References