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The management of proteinuria in diabetes

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The development of proteinuria in a person with diabetes remains the basis of a diagnosis of clinical or overt nephropathy. The appearances of circulating proteins in the urine is mostly dependent upon the permeability of the glomerular basement membrane (GBM), but intra-glomerular capillary pressures and blood flows are also important.

Thickening of the GBM is an early pathological feature of diabetic nephropathy.[1] This is a result of an accumulation of matrix proteins, due to a combination of excess production and decreased breakdown. Excess production may be a response to increased tension in the capillary wall secondary to haemodynamic forces, whereas the decreased breakdown may be secondary to glycaemia-induced inhibition of proteinases. Moreover, glycation of the matrix proteins alters their conformation and electrostatic charge and may prevent enzyme breakdown. The net result of these processes is to make the membrane more permeable to macromolecules, initially to smaller charged proteins, such as albumin, but later to largely more neutral molecules such as immunoglobulins.[2]

In parallel, and perhaps partly causing these pathological changes, are increases in glomerular capillary pressures and flows which animal studies have shown to be a result of afferent and efferent capillary vasodilatation.[3] The afferent capillary appears to be more dilated, thus leading to a net increase in intraglomerular capillary pressure. These changes lead to an increase in glomerular filtration rate – so called hyperfiltration – which has long been recognised as a feature of newly diagnosed human diabetes.

Lowering systemic (and by inference, intraglomerular capillary) blood pressure reduces proteinuria in diabetic and other nephropathies.[4] The development of drugs that inhibit angiotensin II production by blocking the renin angiotensin system (RAS) are particularly effective in this regard. Early clinical observations led to the discovery of activation of the local RAS in the diabetic kidney, and that blockade reduced both hyperfiltration and capillary pressure by reversing arteriolar vasodilatation.[5] Moreover, the demonstration of angiotensin II receptors on glomerular podocytes suggests another mechanism whereby RAS blockade may reduce proteinuria.

The development of sensitive assays for albumin revealed that diabetic patients had increased albuminuria as an early feature of nephropathy.[6] This discovery led to the concept of microalbuminuria or incipient nephropathy, now conventionally defined as an excretion rate of 20–200 μg/min (30–300 mg/day). Microalbuminuria thus provided a surrogate marker for nephropathy and its reduction has been used as a measure of clinical efficacy in nephropathy treatment and prevention.

Use of RAS blocking drugs (specifically angiotensin-converting enzyme inhibitors (ACEI)) in type 1 diabetes has not been shown to prevent the development de novo of microalbuminuria.[7] In hypertensive type 2 patients, however, trandolapril was effective in reducing the incidence of microalbuminuria.[8] Meta-analysis of studies of ACEI in microalbuminuric type 1 patients has shown a 60% reduction in progression to clinical proteinuria (urinary albumin excretion >300 mg/day) and a more than three-fold increase in the likelihood of reverting to normoalbuminuria.[9] In hypertensive microalbuminuric type 2 patients the angiotensin receptor blocker (ARB), irbesartan, achieved similar results.[10] It is notable in both these reports that high doses of the RAS blocking drugs were required. None of these reports, however, reduced the rates of end-stage renal failure or cardiovascular disease. In type 1 diabetic patients with clinical proteinuria, captopril significantly reduced the numbers doubling their baseline serum creatinine (equivalent to halving glomerular filtration rate) by almost 50%.[11] In type 2 diabetes, ARBs had a smaller but still significant effect on the main endpoint.[12,13] Interestingly both studies found a correlation between the magnitude of proteinuria reduction and the effect on doubling of serum creatinine.

Taken together, these studies have led to a near universal adoption of RAS blockade as first-line therapy for diabetic patients with hypertension and/or increased albuminuria.[14] They represent a classic example of how a clinical observation of efficacy leads to greater understanding of basic physiology which leads to better drug targeting and dosimetry. As a consequence of these treatments and other interventions the average period between development of clinical proteinuria and end-stage renal disease has doubled from 7 to 14 years over the last 30 years.[15] This is truly a 'career lifetime advance'.

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New oral agents for type 2 diabetes

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During the past half-century, oral antidiabetic drugs have played a major role in the treatment of type 2 diabetes. First came the biguanides, ie phenformin, metformin and buformin, and the first generation of sulphonylureas, ie tolbutamide, chlorpropamide and tolazamide.[1] It is a testament to their efficacy and safety, if used appropriately, that both classes are used extensively even today. Modern sulphonylureas offer easier dosing regimens, improved safety profiles and a minimal risk of idiosyncratic reactions; as a consequence, these have largely replaced the progenitors. Metformin (dimethylbiguanide) is now the only biguanide currently in use in the UK, phenformin (phenylethybiguanide) having been withdrawn in the 1970s due to an unacceptable risk of lactic acidosis.[2] The United Kingdom Prospective Diabetes Study (UKPDS), which reported its findings in 1998, bolstered the role of metformin. The drug was unique in significantly reducing myocardial infarction and diabetes-related deaths in overweight and obese patients randomised to the drug as monotherapy.[3] Various modified release preparations of metformin and some sulphonylureas as well as fixed-dose combinations of these and other agents have become available in recent years.

So what is new in the armoury of oral drug treatment for type 2 diabetes? Three new classes of oral antidiabetic drugs shown below have been introduced in the last decade or so.[4]

- *α–glucosidase inhibitors.* These agents retard the absorption of carbohydrates by inhibiting brush border enzymes of the small intestine, their greatest affinity being for glycoamylase. Acarbose, a pseudo-tetrasaccharide, was introduced in the UK in the early 1990s and remains the only example of this class available in this country; miglitol and voglibose are available elsewhere. Acarbose failed to take off in the UK largely because of unpleasant – and rather antisocial – gastrointestinal side effects allied to glucose-lowering effects that are generally accepted as being inferior to other oral antidiabetic agents.[5] On the positive side, acarbose has a good safety profile, reflecting low (<2%) systemic absorption of the drug. A recent multinational clinical trial of acarbose created a stir in the diabetes community: not only did acarbose retard the progression from impaired glucose tolerance to type 2 diabetes in high-risk subjects, the incidence of myocardial infarction and new cases of hypertension were also apparently reduced when compared with placebo.[6] However, the study has attracted criticism for failings in design and analysis[7] and a renaissance for acarbose seems unlikely.
- *Rapid-acting insulin secretagogues.* These agents, sometimes called meglitinide analogues, provide an alternative to sulphonylureas. By causing prompt and relatively short-lasting release of insulin from islet beta-cells, repaglinide and nateglinide preferentially reduce the rise in postprandial glucose concentrations.[8] The drugs offer a low risk of severe hypoglycaemia and flexibility for patients whose mealtimes are unpredictable. However, they are expensive compared with generic sulphonylureas and their use necessitates multiple daily dosing. Neither has been enthusiastically embraced in the UK.
- *Thiazolidinediones.* Also known as glitazones, these drugs arrived as the mammoth enterprise that was the UKPDS was coming to a close. These drugs have made the greatest impact on clinical practice of the three classes, but they have generated a fair amount of controversy along the way. Thiazolidinediones are synthetic agonists for the nuclear receptor peroxisome proliferator-activated receptor (PPAR)-gamma, the role of which in human metabolic