Microalbuminuria and nephropathy in insulin dependent diabetes mellitus

Diabetic nephropathy is an important cause of morbidity and mortality in insulin dependent diabetes mellitus (IDDM). The patients at greatest risk of developing diabetic renal disease are those who develop IDDM in childhood. Longitudinal epidemiological studies have shown that individuals with IDDM have a cumulative incidence of nephropathy of 30–50% after 40 years of disease. Therefore in Britain alone it is estimated that 750,000 people have diabetic renal disease with approximately 600 patients entering end stage renal failure each year. As a contributor to the adult programme from end stage renal disease, diabetes exceeds all forms of glomerulonephritis added together and as a single cause it is rivalled only by hypertension. As the development of renal complications poses a serious threat to the life and wellbeing of the diabetic patient, its prevention or amelioration by treatment is an important goal. Microalbuminuria is presently felt to be the most reliable indicator of adverse renal and cardiovascular events in diabetes, therefore screening for its presence is an important part of the management of these patients.

Factors predisposing to diabetic nephropathy

The results of the Diabetes Control and Complications Trial Research Group have confirmed that poor glycaemic control is a major risk factor for the development of diabetic...
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nephropathy. However, not all patients with poor glycaemic control develop nephropathy suggesting that only a subset of diabetic patients are at risk from this complication. This has prompted a search by many investigators for other possible positive predictive factors. Those that have been identified include age at diagnosis and diabetes duration, relative insulin resistance, increased sodium-lithium countertransport, smoking, family history of diabetic nephropathy, and a history of hypertension. The most recent studies, however, seem to indicate that hypertension is in itself not a risk factor for initiating nephropathy, but develops as a consequence of it.

Pathogenesis

Although the clinical course of diabetic nephropathy has been well described, its pathogenetic mechanisms are less well understood. A number of related hypotheses have been proposed which involved a combination of haemodynamic and metabolic factors and are based on the abnormalities observed under experimental conditions in isolated tissues and animal models or early in the course of disease in man.

The central features of diabetic vascular complications are an abnormal leakage of proteins from the circulation and progressive luminal constriction of the blood vessels. Abnormalities of capillary basement membranes including the glomerular basement membrane have been extensively studied in patients with IDDM as has mesangial composition and size. Glomerular basement membrane consists primarily of type IV collagen, hyaluronic acid, the protocollagen heparan sulphate and laminin, the major non-collagenous protein. Heparan sulphate is synthesised by the endothelial cells and is highly negatively charged.

Decreased levels have been found in the glomerular basement membrane in both animals and humans with diabetes. This decrease is apparently not due to a failure of production of heparan sulphate, but because less of it is incorporated into the glomerular basement membrane. Incorporation is dependent on the ligand binding properties of laminin. This binding affinity is reduced by the increased non-enzymatic glycosylation of laminin found in diabetes. As charge is an important factor in the integrity of the endothelium and glomerular basement membrane, decreased heparan sulphate could contribute to the increased vascular permeability and increased glomerular filtration rate (GFR) of negatively charged proteins such as albumin observed in diabetes. Extravasation of plasma proteins into the mesangium might contribute to the mesangial expansion and progressive glomerular damage which results in glomerulosclerosis. The glomerular filtration surface then becomes reduced eventually leading to a fall in GFR.

As early as the onset of diabetes an increase in GFR can be detected. It decreases toward a more normal value with better metabolic control. Hyperfiltration may return later in the course of the disease and has been found to be predictive of the development of later nephropathy by some investigators but challenged by others. Hyperfiltration is due to a combination of increased renal blood flow, increased transglomerular hydraulic pressure, and increased filtration area and has been centrally implicated in the pathogenesis of nephropathy by Hosteller et al. They provide evidence that hyperfiltration results in glomerular damage and proteinuria. Glomerulosclerosis ensues with accompanying loss of renal function.

Classification of diabetic nephropathy

In 1982, Viberti et al reported that patients with IDDM who were at risk of clinical nephropathy could be identified at an early stage by detecting small increases in urinary albumin excretion (UAE), a phenomenon named microalbuminuria. Its presence characterises the stage of incipient nephropathy. Over the last decade, several studies have been performed to investigate the predictive power of microalbuminuria for clinical proteinuria, chronic renal failure, morbidity, and mortality in IDDM. After completing a 23 year follow up study, Messent et al concluded that microalbuminuria was presently the most reliable indicator available to the clinician of adverse renal and cardiovascular events in diabetic patients. By general consensus, microalbuminuria is defined in the adult as a UAE of 20–200 μg/min (or 30–300 mg/24 hours) in a timed overnight collection in two out of three urines collected consecutively preferably within a six month period. This supranormal quantity of urinary albumin escapes detection by indicator dye binding tests such as those used in reagent strips like Albustix (Bayser). Above this level, Albustix testing becomes positive and the patient is then classified as having overt nephropathy. It is during this phase that there is persistent proteinuria, a fall in GFR and development of renal failure. Without treatment, the outlook for these patients is poor with 50% dying within seven years.

Screening for microalbuminuria

Measurement of UAE in timed urine samples remains the gold standard for the definition of microalbuminuria. However, as timed and measured urine collections can be difficult, especially in children, this precludes their use as a routine screening procedure. Attempts have therefore been made to relate either the albumin concentration or albumin-creatinine ratio (UA/UC) to UAE in random or first morning urine specimens. Using random urine samples, Gatling and colleagues reported only weak correlations of urinary albumin concentration and UA/UC with albumin excretion rate in a timed overnight collection (r=0.45 and 0.43 respectively). However, if the albumin concentration or UA/UC was measured in an early morning urine sample, the correlation with the overnight albumin excretion rate was stronger (0.90 and 0.91 respectively). Taking a UA/UC value of 3.5 mg/mmol in an early morning sample to predict an overnight albumin excretion rate of 30 μg/min gave a sensitivity of between 88–100% and specificity of 95–99%. The most reliable method of screening for microalbuminuria is therefore felt to be the measurement of UA/UC in an early morning (first void) urine sample. The use of albumin concentration or UA/UC in a random urine sample is not recommended because of unacceptably low sensitivity and specificity in predicting microalbuminuria.

There remains some debate as to whether all diabetic patients should be screened for microalbuminuria. Screening should certainly focus on those with an early age at onset of diabetes, duration of diabetes greater than five years, hypertension, persistent hyperglycaemia (glycated haemoglobin >11%) or any evidence of retinopathy or neuropathy.

Microalbuminuria in children

A general consensus has been reached for the quantitative definition of microalbuminuria in adults, but this has not been the case in paediatrics. In the few studies that have investigated albumin excretion in the urine of normal children, the upper 95% tolerance limit has been used as the lower limit of definition for microalbuminuria. In these early studies, the values reported lay between 7 and 12.2 μg/min/1.73 m². It can be seen that these values lie...
below the defined predictive levels for microalbuminuria quoted in adult studies. The significance of having an albumin excretion rate above normal but below 20 µg/min is not known as no long term predictive work following on from these initial studies has been reported. A more recent study of albumin excretion rate in children has used 20 µg/min as the lower limit of definition of microalbuminuria.\textsuperscript{43}

The prevalence of microalbuminuria in children with diabetes is reported to be between 7–20%, the exact value depending upon the cut off point for defining microalbuminuria.\textsuperscript{41-45} The prevalence increases with the age of the population under study. This is probably explained not only by the increased disease duration in the older children, but also because of the observation that children seem to be relatively protected from developing the complications of diabetes before the onset of puberty, thus calling into question the role of growth hormone and sex steroids in their development.\textsuperscript{40 42 46}

**Following up microalbuminuria**

The upper reference limit for microalbuminuria is quoted as an early morning UA/UC >1.5 mg/mmol.\textsuperscript{47} Repeated testing of diabetic patients for microalbuminuria reveals that many are only intermittently positive.\textsuperscript{48} If microalbuminuria is detected on three successive occasions, it is considered persistent and approximately 80% of these patients will go on to develop overt nephropathy. This progression has been reported to take between 13 and 18 years, although it may occur faster in some patients.\textsuperscript{35 49}

It is recommended that patients with UA/UC values between 1.5–3.5 mg/mmol should have their UA/UC values repeated annually. Patients with UA/UC values >3.5 mg/mmol should have timed overnight urine collections performed to confirm the diagnosis of microalbuminuria and UA/UC ratios measured 4–6 monthly. A value of UA/UC >3.5 mg/mmol obtained on repeated testing should identify those patients who would benefit from specific treatment. Close monitoring (every three months) of the response of UAE to treatment is important.

**Potential treatment for the prevention of diabetic nephropathy**

The controversy about whether improvement in glycaemic control would substantially reduce the risk of development and progression of diabetic retinopathy, nephropathy, and neuropathy finally ended with the publication of the Diabetes Control and Complications Trial Report in 1993.\textsuperscript{5} In a group of highly motivated volunteers aged 13–39 years it convincingly demonstrated that intensified glycaemic control would reduce the risk of complications in all patients with diabetes. The patients receiving intensive treatment attended clinic monthly, had frequent reviews by telephone, and 24 hour access to medical advice. The glycated haemoglobin level was measured monthly and the patients monitored their own blood glucose concentration four times daily. Insulin was administered in three or more injections per day and the dose was altered according to the frequently monitored blood glucose values. Achieving this tight control (that is, near normoglycaemia) in young children would neither be possible nor desirable because of the risks of severe hypo- and hyperglycaemia. Improving glycaemic control in our adolescent diabetics requires a great deal of effort on the part of both the patients and those who care for them. This would require a substantial increase in the medical and paramedical input into their day to day care with huge financial implications to the NHS. Although every effort should go into improving glycaemic control, the benefits against the risks have to be balanced and the treatment strategy must be tailored for the individual patient.

Apart from improving blood sugar control there are other potentially beneficial treatment modalities. The effects of angiotensin converting enzyme (ACE) inhibition have been found to be beneficial both in overt and incipient nephropathy with and without hypertension.\textsuperscript{50–52} The results of the European Microalbuminuria Captopril Study Group reported that captopril treatment significantly impeded progression to clinical proteinuria and prevented the increase in albumin excretion rate in non-hypertensive adult diabetics with persistent microalbuminuria.\textsuperscript{52} In the only study reporting the use of ACE inhibitors in normotensive diabetic children with microalbuminuria, Cook \textit{et al} found that captopril was effective in decreasing albumin excretion rate.\textsuperscript{53} Data from an animal model of diabetes suggest that ACE inhibition may directly reduce intraglomerular pressure by selective vasodilatation of the efferent arteriole and, in doing so, reduces proteinuria.\textsuperscript{54} ACE inhibitors may also have an effect on glomerular hypertrophy and mesangial matrix formation and therefore they may have other benefits to the diabetic kidney independent of their antihypertensive effect.\textsuperscript{55 56} This makes this group of drugs the ones of choice in treating hypertension in diabetes.

In addition to the above therapeutic measures, a reduction in dietary protein has been shown to have a beneficial effect in diabetes with renal disease as a high protein intake is known to increase the GFR and increase intraglomerular pressure.\textsuperscript{57 58} However, protein restricted diets are unpleasant to take and compliance in diabetic children would be a major problem.

**Conclusion**

As microalbuminuria has been established as a powerful marker of both early nephropathy and premature cardiovascular disease in diabetes mellitus, screening for microalbuminuria in children and adolescents with diabetes is recommended. The first step in treatment of a persistently elevated UA/UC value in an early morning urine sample should aim at achieving better metabolic control if possible. Although the short term use of ACE inhibitor drugs in normotensive children has been shown to be beneficial in one study, the outcomes of further studies are required before their use can be recommended for all diabetic children with microalbuminuria. In children with diabetes and hypertension they should be the antihypertensives of choice. As the risk of nephropathy and premature death is a long term one, many years will elapse before the full implications of screening for microalbuminuria and intervention programmes are realised.

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