Diabetic nephropathy is a distinct pathological condition seen in both types of diabetes (ie, type 1 and type 2). Not all diabetic patients with chronic kidney disease (CKD) have diabetic nephropathy as a cause. Diabetes mellitus (DM) can also cause kidney damage via other disease processes. Patients may suffer from repeated urinary tract infections and these episodes may lead to recurrent and chronic pyelonephritis that may damage and decrease renal mass. For cases complicated by neurogenic bladder, painless obstructive uropathy may be present long before diagnosis is made, causing asymptomatic progressive renal impairment.

Many diabetics share similar cardiovascular (CV) risks factors such as hypertension and dyslipidaemia. Together, all these factors may lead to diffuse small vessel disease and a condition known as ischaemic nephropathy (recurrent renal ischaemia and asymptomatic small infarctions). Diabetic nephropathy and ischaemic nephropathy account for the majority of CKD in the diabetic population.

Diabetic nephropathy is usually suspected by screening blood and urine tests. It must be remembered that as type 1 diabetes mellitus (T1DM) is diagnosed at the onset of disease, nephropathy is not seen in the first decade of the disease. However, the situation is quite the opposite for type 2 diabetes mellitus (T2DM). Many with T2DM may have had undiagnosed DM for a significant period of time and present with complications of DM when it was first diagnosed. Hence, all newly diagnosed T2DM patients must be screened for possible kidney disease at the same time.

Microalbuminuria and Macroalbuminuria
We understand hyperglycaemia initially leads to nephromegaly and hyperfiltration. Many in the early stages of the disease may have higher than normal glomerular filtration rate (GFR) or hyperfiltration. Hyperfiltration is induced by a rise in intraglomerular pressure (this is the pressure within each glomerulus in the kidney). Chronic hyperfiltration is associated with eventual structural change and damage to the kidneys. Treatment with an agent that inhibit the renin-angiotensin system (RAS) will negate the raised intraglomerular pressure and preserve kidney function in the long term.

An early clinical manifestation of diabetic nephropathy is microalbuminuria – a very small quantity of albumin leaking into the urine. The normal rate of albumin excretion in the urine is less than 30mg/day (20mcg/min). Microalbuminuria is defined as

30-300mg/day of albuminuria (20-200mcg/min). Screening for microalbuminuria is the best method to detect possible early diabetic nephropathy. This can be done with a spot urine (preferably early morning first void) sample. It can be sent to the lab for urinary albumin-creatinine ratio or tested in the clinic using a special strip that can detect albuminuria in this range. Usual dipstick used in clinics can only detect macroalbumiuria – quantity of albuminuria exceeding 300mg/day or 200mcg/min.

24-hour urine collection is the gold standard but it may not be practical for many, especially older patients (who are forgetful and/or may have incontinence). In addition to predicting risk for eventual overt diabetic nephropathy, presence of microalbuminuria is also associated with risk of CV disease. The small quantity of albuminuria is thought to reflect endothelial dysfunction and not just renal disease. Many best practice guidelines advocate early detection of microalbuminuria in diabetic patients.

Progression of microalbuminuria to macroalbuminuria is estimated to be in the range of 2.5-3%/year. The onset of macroalbuminuria is usually associated with reduction in renal function, ie, reduced glomerular filtration rate (GFR). Long-term observational studies have noted a decline of 1ml/min/month in diabetics with macroalbuminuria. If the condition is left untreated, progression to end-stage kidney failure will be the inevitable consequence.

It is important to know that albuminuria may occur in other forms of renal disease apart from diabetic nephropathy. Albuminuria that occurs very early (less than five years) in the course of T1DM is not due to diabetic nephropathy. A patient who presents with sudden nephrotic syndrome with preserved (normal) GFR is likely suffering from a form of glomerulonephritis and not diabetic nephropathy. This also applies to a patient with albuminuria and with significant haematuria (diabetic nephropathy is classically a solely proteinuric/albuminuric disease). A patient with acute sudden decline in renal function will also require further evaluation beyond a presumed diagnosis of diabetic nephropathy. Any other associated features not expected in a diabetic will also be a cause for suspecting that it is not diabetic nephropathy. Presence of diabetic retinopathy supports a diagnosis of diabetic nephropathy but absence does not rule it out completely in T2DM patients, as concordance of both these microvascular complications is lower in T2DM.

Preventing the Progression of Microalbuminuria
Having screened or made a diagnosis, executing the right treatment strategy is crucial to reduce the risk of worsening kidney disease. Treatment has been shown to regress microalbuminuria to normoalbuminuria in some patients if the condition is diagnosed early in the microalbuminuria phase. Patients who are able to regress to normoalbuminuria have much lower risk of morbidity and mortality related to CV and renal events. Even if treatment does not lead to regression to normoalbuminuria, it can retard and reduce progression to macroalbuminuria and overt renal disease.

There exist good evidence that diabetic nephropathy can be treated and the progression of disease can be retarded to some extent. Effective measures to delay progression of diabetic nephropathy should be...
started as early as possible. Many best practice guidelines advocate for regular and programmed urinary screening for patients with DM (with the exception of the first five years in patients with T1DM). Microalbuminuria is the first sign of diabetic nephropathy and past trials have shown that intervening in this group of patients will reduce the risk of developing overt diabetic nephropathy.

Primary prevention aims to modify or prevent development of risk factors that lead to eventual diabetic nephropathy and end-stage kidney failure. Two major risk factors contributing to this are poor glycaemic control and development of microalbuminuria. As such, the chief means of delaying or preventing onset of diabetic nephropathy is to have stringent glycaemic control and therapy to prevent onset of microalbuminuria.

Glycaemic control has been well proven to prevent onset and delay progression of diabetes-related renal complications. It can at least partially reverse glomerular hypertrophy and hyperfiltration – both hallmarks of early diabetic kidney disease. It also delays the appearance of albuminuria and reduce the degree of albuminuria for those with pre-existing significant albuminuria. Achieving euglycaemia should always be the aim for all diabetic patients, perhaps with the exception of the elderly and those with advanced renal impairment. Past studies demonstrated efficacy using insulin in T1DM and various oral diabetic agents in T2DM. The strongest evidence of reversibility is in patients receiving pancreatic transplantation (curative treatment) showing glomerular structural improvement after 10 years post-transplant. Choice of therapy to achieve normoglycaemia is less important than the ability to reach target glycaemic control. A target HbA1c of 7% is very reasonable although in a recent large trial of intensive glycaemic control, achieving HbA1c of 6.5% was associated with better outcome especially in preventing the onset of microalbuminuria, hence reducing the risk to developing overt diabetic nephropathy.

Clinical Trials

ADVANCE (Action in Diabetes and Vascular Disease: Preterex and Diamicron MR Controlled Evaluation)

The ADVANCE trial was conducted to determine if more intensive glucose control with HbA1c below 6.5% and routine blood pressure-lowering using angiotensin-converting enzyme inhibitor (ACEi) will reduce the risk of developing micro and macrovascular complications in T2DM patients. With 11,140 diabetic patients enrolled from over 20 countries, the study demonstrated a very encouraging 21% relative risk reduction in preventing microalbuminuria in the intensive glucose control group.

BENEDICT (Bergamo Nephrologic Diabetes Complications Trial)

This trial, with more than 1,200 T2DM patients enrolled from centres in Italy, showed that ACEi trandolapril, but not non-dihydropyridine calcium blocker verapramil SR, significantly reduced the risk (by about 50-60%) of developing persistent microalbuminuria in T2DM. Subsequent post-hoc analysis identified only patients with systolic BP above 139mmHg derived an advantage using ACEi in preventing the onset of microalbuminuria.

ROADMAP (Randomized Olmesartan and Diabetes MicroAlbuminuria Prevention) Trial

More recently, the primary prevention trial ROADMAP was completed.
and results published in the New England Journal of Medicine. The trial enrolled 4,447 T2DM patients with at least one CV risk factor. Patients were randomised to receive either olmesartan (40mg daily) or placebo. Olmesartan is a long-acting angiotensin receptor blocker (ARB). The tolerance for ARB is considered superior to that of ACEi as there is significantly lesser incidence of cough and angioedema. The intended target blood pressure (BP) for this trial was below 130/80mmHg. Patients were allowed to receive other antihypertensive agents (but not a renin-angiotensin blocking agent) to achieve the intended target BP.

The patients enrolled had an average age of about 58 years old, BMI of 31, estimated GFR of 85ml/min, HbA1c of 7.6%, and urine albumin:creatinine ratio (UACR) of 4 mg/g. Over 80% of the patients fulfilled the criteria of metabolic syndrome with an average DM vintage of just over six years. The mean baseline systolic BP was 136-137mmHg and mean baseline diastolic BP was 80-81mmHg. The majority of the final trial population had three to five CV risk factors and 80% of them were on antihypertensive agent(s).

Over a median follow-up of 3.2 years, olmesartan delayed the onset of microalbuminuria by 23% when compared to placebo. The study also found that patients with higher baseline systolic BP (>135mmHg) and those with higher UACR (>4mg/g) – although still within the normoalbuminuria range – are more likely to benefit from the active treatment. Patients with better glycaemic control (HbA1c<7.3%) are also more likely to show a positive result. To date, ROADMAP is the only randomised clinical trial using an ARB to demonstrate the effect of delaying onset of microalbuminuria in T2DM patients as a primary outcome.

It must be cautioned that patients with pre-existing coronary heart disease (CHD) tolerate aggressive BP reduction less well. The risk of hypotension is higher with olmesartan than in the placebo group. One of the findings in the ROADMAP trial was the slightly increased rate of adverse CV outcome if the systolic BP was below 122mmHg or when there was more than 17mmHg reduction from baseline in the group with pre-existing CHD. This trend is consistent with results seen in other CV trials. The 2009 ESH/ESC reappraisal of European Guidelines on Hypertension Management also highlights the concerns about the overtreatment of high BP that is – physicians should avoid treating BP to values below 120/70mmHg in patients with underlying CHD. Otherwise, the treatment with olmesartan was well tolerated and comparable to the placebo group.

Conclusion
With an estimated worldwide population of 350 million diabetics (mainly T2DM) presently, there is a strong and urgent need to prevent onset of target organ damage resulting from DM. The financial and physical costs of diabetic chronic kidney disease are enormous. It is most cost-effective to treat early or better still, prevent the onset of this dreaded condition. At the National University Hospital Singapore, we have continued with the programme designed to retard progression of diabetic nephropathy. Diabetic nephropathy of all stages can be treated and, as shown in the few major trials discussed here, primary prevention is a distinct possibility. There are some who will argue that microalbuminuria is at best only a surrogate marker of diabetic nephropathy and is not a robust end point. Although the definitive proof of successful primary prevention is preservation of renal function in the long term, microalbuminuria is a validated marker of early (diabetic) kidney disease and also CV disease.

In delaying its onset, we hope patients with T2DM will be less fearful of their future. Stringent glycaemic control should be the emphasis for all physicians treating DM. Those with hypertension should be treated with a renin-angiotensin blocking agent, even when they have no significant UACR (normoalbuminuria). The choice of agent to use will be determined by the summation of considerations given to the efficacy, tolerability, and cost of a particular agent.

Further Reading

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