Diabetes and chronic kidney disease

Chronic kidney disease is a common complication of diabetes.

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When insulin was discovered decades ago, the possibility arose that diabetes mellitus could have been cured but, alas, the long-term complications were realised only later. Today diabetic nephropathy (DN) is a leading cause of end-stage renal disease (ESRD) in Western societies.[1] It is the single largest cause of ESRD in adult Americans and Europeans, accounting for over a third of all patients beginning renal replacement therapy. As South Africa becomes more affluent and more inhabitants assume a Western style of living, we can expect a similar situation to develop here. The additional tragedy in our setting is that many diabetics are refused chronic dialysis or transplantation due to significant extrarenal disease, mainly cardiovascular, that precludes renal replacement therapy in the public sector.[2]

Clinical picture and natural course

Both type 1 and type 2 diabetics may develop DN, males have a slightly higher propensity for developing DN and ethnic background may play a role, with native Americans, African Americans and south Asians more likely to be affected.

The hallmark of established DN is proteinuria, often severe enough to be classified as nephrotic syndrome. In the natural history of DN, Mogensen identified 5 stages of renal dysfunction (Table I).[3] These are more clearly defined in type 1 diabetics, mainly because they often present with metabolic complications early after onset of diabetes, while type 2 diabetics may have a very insidious onset and they may have been exposed to a much longer period of hyperglycaemia before the diagnosis is made.

Hyperfiltration

Hyperfiltration is common in early diabetics and is suspected to be due to increased glomerular capillary pressure in the glomerulus, mainly mediated by afferent vasodilatation. It may be partly responsible for progressive renal damage. Measures that reduce glomerular pressure such as reduction of systemic blood pressure, low-protein diet (which blocks afferent arteriolar dilatation) or ACE inhibition (which blocks angiotensin-mediated efferent vasoconstriction) all slow down the development of glomerular damage and proteinuria.[1] The hyperfiltration is associated with hypertrophy (glomeruli) and proliferation (tubulointerstitial structures) with several centimeters' increase in renal size. These changes improve with good glucose control.

Table I. Stages of diabetic nephropathy

- **Stage 1:** Renal hypertrophy and hyperfiltration – glomerular filtration rate may be increased 20 - 40%
- **Stage 2:** Is clinically 'silent' but hyperfiltration persists and is correlated with mild hyperglycaemia
- **Stage 3:** Microalbuminuria is present
- **Stage 4:** Overt nephropathy with proteinuria, hypertension and progressive renal failure
- **Stage 5:** End-stage renal failure develops

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Microalbuminuria (after 5 - 15 years)

Small amounts of normal s-albumin may occur in the urine of healthy non-diabetic persons, but should not exceed 30 mg in 24 hours. The amount may vary by 40% on different days, and is affected by strenuous exercise, oral protein intake, fluid loading, urinary tract infection and pregnancy. On average urinary albumin excretion rate (UAER) is 25% higher during the daytime. To make the diagnosis of microalbuminuria, 2 of 3 consecutive collections in a 3-month period should be in the microalbuminuric range (30 – 300 mg/24 h). It is more practical to use the urine albumin creatinine ratio (ACR) on early-morning urine, because it obviates the need for a timed urine sample. Values above 2.5 mg/mmol are indicative of microalbuminuria.

Screening

All type 1 diabetics over 12 years of age should be screened annually for microalbuminuria from 5 years after the diagnosis of diabetes has been made, while type 2 diabetics should start immediately with annual screening. If the morning AER is elevated it should be confirmed with timed specimens and followed 6 monthly. Patients

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with microalbuminuria should receive a drug acting against angiotensin, irrespective of blood pressure.

Associated conditions

- **Microangiopathy.** The glomerular filter consists, among others, of a tuft of capillary vessels that forms part of the filter in the kidney. In healthy persons, molecules from the size of albumin and larger are prevented from passing into the urine by these structures. Early disease of small blood vessels (endothelial dysfunction) can thus be detected by the presence of albumin in the urine, and correlates with clinical evidence of microangiopathy (retinopathy and neuropathy). One of the few places where small blood vessels can be observed directly is in the retina – clinicians should therefore not lose their ability to use an ophthalmoscope.
- **Hypertension.** Blood pressure tends to rise once proteinuria becomes evident, and the normal nocturnal dipping of blood pressure on ambulatory monitoring becomes less. An important mechanism of hypertension is sodium and water retention with volume-mediated hypertension.
- **Cardiovascular disease.** The presence of microalbuminuria is a predictor of cardiovascular morbidity and mortality, including coronary heart disease, silent myocardial ischaemia and left ventricular hypertrophy.
- **Hyperlipidaemia.** Hypertrygliceridaemia, lower HDL and higher LDL cholesterol occur as microalbuminuria increases. These should be managed in their own right.

Overt proteinuria

When diabetic patients develop proteinuria the clinical question usually arises whether diabetic nephropathy can be accepted and whether the patient should have a renal biopsy or other investigation to exclude other treatable renal disease. The usual indications[1] for a biopsy or other investigations are summarised in Table II.

Important other renal conditions occur in diabetics and should be kept in mind:

- renal papillary necrosis
- renovascular disease
- autonomic neuropathy of the bladder
- urinary tract infections
- contrast nephrotoxicity.

Renal failure

End-stage renal failure occurs a median of 7 years after overt proteinuria.

As renal function declines, two things happen that may give patients the impression that they are improving, while in fact the opposite may be true. Less insulin may be required daily to control the sugar due to less catabolism of insulin in the diseased kidney, and the nephrotic syndrome may improve clinically (less swelling) because the surface area for filtration of the glomeruli is diminishing. Diabetic nephropathy is one of the causes of patients presenting with end-stage renal disease and relatively normal-sized kidneys. All forms of renal replacement therapies may be used in diabetics including successful renal (and sometimes simultaneous pancreas) transplantation.

Predialysis care and problems related to renal replacement therapy in diabetics

- Blindness due to retinopathy may preclude peritoneal dialysis if a family member is not available to help, so regular retinal care by an ophthalmologist is essential.
- Macrovascular disease creates problems in making effective fistulae for haemodialysis. The additional burden of coronary heart disease and stroke is worsened by renal failure that may promote atherosclerosis. Good care to modify atherosclerotic risk factors should be initiated early in diabetic management. Cessation of smoking is particulary important because smoking is an independent risk factor for progression of renal failure, and also affects atherosclerosis.
- Neuropathy, both peripheral and autonomic, may be worsened by renal failure and can cause problems with blood pressure control on dialysis, nausea and vomiting due to gastroparesis and orthostatic hypotension.
- Anaemia and bone disease management should not be neglected.

Management of diabetic renal disease

In our armamentarium we have glucose control, antihypertensive treatment, particularly targeting the renin-angiotensin system and restriction of dietary protein.

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Table II. Indications for renal biopsy or other investigations in diabetic renal disease

- The absence of retinopathy, specifically in type 1 diabetics
- Rapid onset of severe proteinuria, with a short duration of diabetes (< 5 years) (type 2 diabetics may have proteinuria soon after the diagnosis is made)
- With macroscopic haematuria – microscopic haematuria does occur in diabetic nephropathy, but macroscopic haematuria may indicate papillary necrosis or a glomerulonephritis (IgA)
- Active urinary sediment, particularly red cell casts
- Rapid decline in renal function without significant proteinuria, particularly in type 2 diabetics when atherosclerotic renovascular disease should be considered; usually a Doppler investigation of renal arteries, or an MR angiography are done as screening tests
- If serological tests suggest another disease (such as antinuclear factor (ANF), antineutrophil cytoplasmic antibody (ANCA), etc.)

Glycaemic control

Although good glucose control is important in all diabetics, we have good evidence that, particularly in early disease, it may prevent progression. The DCCT trial showed that normoalbuminuric patients had a smaller chance of developing microalbuminuria with tight glucose control. When microalbuminuria and later overt nephropathy occur, the effect of good glucose control, although probably still beneficial, is not so clear and the effect of hypertension may start to predominate.

Antihypertensive therapy

Hypertension (BP > 140/90 mmHg) usually starts within a few years of the onset of microalbuminuria, and control of blood pressure has been shown to have a major beneficial effect on proteinuria and preservation of renal function. A lower threshold for starting antihypertensives (130/80 mmHg) and a lower target blood pressure[4] are advocated by most guidelines in use today. How low to go is not absolutely clear at this stage, but the more proteinuria is present, the lower a target should probably be chosen. There is some evidence that all antihypertensives are not equal and those affecting the renin-angiotensin system are of particular benefit.

ACE-inhibitors and angiotensin receptor blockade (ARB)

Few studies are available in normotensive diabetics with normoalbuminuria that show benefit in preventing the onset of microalbuminuria by early use of ACE-inhibitors. However, several studies have documented their beneficial effect once microalbuminuria occurs, even without hypertension, and they may delay the onset of overt proteinuria. Most studies with ACE-inhibitors have been done in type 1 diabetics but several studies with type 2 diabetics using ARBs are available with similar results. The DETAIL[5] trial compared an ACE-inhibitor with an ARB directly in type 2 diabetics and found them equally effective. To control proteinuria it may be necessary to use a combination of an ACE-inhibitor and an ARB. However, the development of hyperkalaemia may be prohibitive, particularly in those patients with hyporeninaemic hypoaldosteronism.

Table III. Management of diabetic nephropathy in a nutshell

Stage	Management	Monitor
Early microalbuminuria	Optimise glycaemic control ACE–inhibitor or ARB (even with normal BP)	HbA_{1c} < 7% Urine prot/creat ratio
Proteinuria	Aggressive BP control	BP < 130/80 or less
Renal failure	0.8 g/kg/day protein restriction Early dialysis	Risk factors for atherosclerosis

Dietary protein intake

Dietary protein restriction may improve uraemic symptoms and in some instances retard progression of renal disease, although this was not proven in all studies. The problem is that patients who are malnourished (as evidenced by hypoalbuminaemia) and who are started on dialysis, do worse on renal replacement therapy. Most nephrologists advocate a protein restriction of 0.8 g/kg/day with care not to allow the patient to become malnourished. Although it is generally suggested that a diabetic with stage 5 renal failure should be started earlier on dialysis, in South Africa most of these patients in the public sector are refused chronic dialysis – therefore dietary protein restriction will remain part of our management.

Table III summarises the management of diabetic nephropathy.

Conclusion

Clinicians have an added responsibility to optimise care of diabetic patients in South Africa, because renal replacement is not an option for a significant group of these patients. We should always control glucose as well as possible and start an ACE-inhibitor when microalbuminuria occurs, irrespective of the blood pressure. When overt nephropathy occurs, meticulous blood pressure control (using drugs acting against angiotensin, among others), is necessary, regularly monitoring both blood pressure and proteinuria, with targets of blood pressure lower than those of the general hypertensive population. Even if the blood pressure is controlled medication may have to be increased further to reduce proteinuria. All possible modifiable risk factors for atherosclerosis should be identified and controlled. Any unnecessary additional insults to the kidneys should be avoided when possible, such as contrast-induced nephrotoxicity, analgesics, NSAIDs and aminoglycosides. Timely preparation for early renal replacement therapy should be started in the fortunate patients who have this option available.

References

1. Johnson R, Feehally J. *Comprehensive Clinical Nephrology*, 2nd ed. Mosby, 2003.
2. Department of Health. Criteria for chronic dialysis. Policy document, 1997.
3. Mogensen CE. How to protect the kidney in diabetic patients with special reference to IDDM. *Diabetes* 1997; 46 (suppl 2): 104-111.
4. Joint National Hypertension Guideline Working Group. South African Hypertension Guideline 2006, *S Afr Med J* 2006; 96 (part 2): 337-362.
5. Barnett AH, Bain SC, Boulter P, *et al*. ARB versus ACE inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004; 351: 1952-1961.