

The shifting paradigm of albuminuria in diabetic kidney disease

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Diabetic kidney disease has been traditionally thought of as being a linear progression from microalbuminuria to macroalbuminuria to renal failure. New emerging concepts have proved this to be incorrect and are changing the way diabetic kidney disease is considered.

KEY POINTS

- Microalbuminuria may be transient and regress. This is more likely to occur if risk factors, such as blood glucose levels, blood pressure and lipid levels, are well controlled.
- Normoalbuminuric (nonclassical) diabetic kidney disease accounts for at least 25% of patients with chronic kidney disease (CKD) and diabetes.
- Although diabetic kidney disease is the most common cause of CKD in a patient with diabetes, other causes should be considered.
- Care of patients with diabetes requires careful attention to modifiable factors such as dyslipidaemia and hypertension, as well as good glycaemic control.

MedicineToday 2015; 16(7): 34-38

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Diabetic nephropathy is a major cause of morbidity and mortality and remains the leading cause of end-stage kidney disease (ESKD) in Australia, accounting for 35% of new cases.¹ Improvements in the treatment of patients with diabetes and hypertension have reduced the proportion of those who develop chronic kidney disease (CKD); however, the increasing prevalence of diabetes in the general population has meant that the incidence of diabetic kidney disease (DKD) continues to rise.²

Diabetic nephropathy has traditionally been thought of as a disease process with a linear progression from microalbuminuria to macroalbuminuria and eventually to renal failure. This article aims to highlight two emerging concepts in DKD: firstly, that diabetic microalbuminuria is often a transient phenomenon that can resolve and in this case does not confer an increased risk of long-term kidney disease; and secondly, the increasing understanding of nonclassical DKD, in which DKD progresses in the absence of proteinuria. Treatment aims for the patient with established DKD, stratified by cardiovascular risk status, will also be discussed.

Classical diabetic kidney disease

The presence of macroalbuminuria and progression of microalbuminuria are associated with an increased risk for developing established DKD.³ Initial studies published in the 1980s suggested that 80% of patients with type 1 diabetes and microalbuminuria progressed to overt proteinuria by 10 to 15 years in the absence of any specific intervention to modulate albumin excretion.⁴ A more contemporary study, based on the long-term follow up of patients with type 1 diabetes and persistent microalbuminuria in the Diabetes Control and Complications Trial (DCCT), has suggested that the 10-year cumulative incidences of progression to macroalbuminuria, impaired glomerular filtration rate (GFR) and ESKD

were 28%, 15% and 4%, respectively, and regression to normoalbuminuria was 40%.⁵ Similar rates of progression from microalbuminuria to macroalbuminuria have been reported for patients with type 2 diabetes, specifically the rate of progression was 28% in one particular study.⁶ This indicates that the prognosis for patients with microalbuminuria is currently much better than that described in earlier studies.

Transient microalbuminuria

The finding of microalbuminuria does not always equate to an increased risk of deterioration in renal function. In some cases, microalbuminuria represents a dynamic process that is more likely to resolve than progress to overt proteinuria. A significant proportion of patients spontaneously revert to normoalbuminuria (<2.5 mg/mmol in men, <3.5 mg/mmol in women) even after two to three years of persistent microalbuminuria. One study found that the development of persistent microalbuminuria in 170 initially normoalbuminuric, normotensive patients with type 1 diabetes revealed four subsequent patterns of albuminuria:⁷

- persistent microalbuminuria in 58% of patients
- intermittent microalbuminuria in 29% of patients
- transient persistent microalbuminuria in 8% of patients (patients who met the criteria for persistent microalbuminuria but reverted to normoalbuminuria)
- persistent normoalbuminuria in 5% of patients.

Importantly in the above study, none of the patients were treated with renin–angiotensin–aldosterone (RAA) blocking agents.⁷

Resolution of microalbuminuria is more likely in patients with lower levels of microalbuminuria and tight control of blood glucose levels, blood pressure and lipid profile levels. The DCCT, which examined the effects of tight glycaemic control early in the course of diabetes, reported a 60% remission rate of microalbuminuria accompanied by a 50% reduction in the risk of impaired GFR.⁸ Similarly, the renoprotective effects of aggressive glycaemic control were observed in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial in patients with type 2 diabetes. In these trials, achieving a glycosylated haemoglobin (HbA_{1c}) measurement of about 6.5% (48 mmol/mol) was associated with delayed progression of albuminuria compared with standard glycaemic control (HbA_{1c} about 7.5% or 59 mmol/mol).^{9,10} In the ADVANCE trial, tight glycaemic control was also associated with a reduced risk of end-stage renal disease.^{11,12}

Although several studies have demonstrated a relation between a decrease in albuminuria within the microalbuminuric range and amelioration of GFR loss, a causal relation between interventions that reduce albuminuria within the microalbuminuric range and a slowing of GFR loss remains to be fully defined.¹³ In the Steno-2



study, intensive multifactorial intervention was associated with a decreased rate of progression from microalbuminuria to overt nephropathy over eight years in patients with type 2 diabetes; however, the rate of decline in isotopically measured GFR was similar in those who received conventional or intensive multifactorial treatment.¹⁴ The relation between a decrease in albumin excretion rate and a slower rate of GFR decline was documented only in a post hoc analysis that pooled results from groups receiving conventional or intensive treatment.¹⁴

Nonclassical diabetic kidney disease

There is now growing appreciation that DKD can also present and progress in the absence of increasing albuminuria. This clinical entity, known as nonclassical DKD or normoalbuminuric renal insufficiency, is now thought to represent at least 25% of cases of CKD in patients with diabetes. These patients have a declining estimated GFR (eGFR) despite remaining normoalbuminuric. Patients with nonclassical DKD are more likely to be older and female, and have lower waist circumferences and higher insulin sensitivities than those who develop albuminuric DKD. Some studies have suggested a more indolent course of renal decline in these patients than in those with classical DKD. However, other studies have shown very similar trajectories of GFR decline, with similar rates of renal replacement therapy and mortality, for patients following the, albuminuric or nonalbuminuric pathway to renal impairment.⁴

Histopathology of diabetic kidney disease

The classic biopsy finding in patients with diabetic nephropathy is nodular sclerosis (Kimmelstiel-Wilson lesions). Nodular sclerosis is responsible for changes ranging from glomerular basement membrane thickening seen on electron microscopy to mesangial expansion, nodular glomerulosclerosis and advanced diabetic glomerulosclerosis.¹⁵ However, many possible findings can be seen

		Albuminuria stage		
		A1	A2	A3
Kidney function stage	GFR (mL/min/1.73m ²)	Normal (urine ACR mg/mmol) Male: <2.5 Female: <3.5	Microalbuminuria (urine ACR mg/mmol) Male: 2.5–25 Female: 3.5–35	Macroalbuminuria (urine ACR mg/mmol) Male: >25 Female: >35
1	≥90	Not CKD unless haematuria, structural or pathological abnormalities present	Yellow	Red
2	60–89			
3a	45–59	Orange	Orange	Red
3b	30–44	Orange		
4	15–29	Red		
5	<15 or on dialysis	Red		

Figure. Classification of chronic kidney disease (CKD) in people with diabetes according to stages of albuminuria and estimated glomerular filtration rate (eGFR). The colour code refers to clinical action plans for management strategies according to CKD stage and cardiovascular risk. Yellow = exclude other treatable causes of CKD; reduce progression, assess cardiovascular risk and avoid nephrotoxins and dehydration. Orange = as for yellow but detect and manage complications of CKD, adjust medication doses if necessary and refer to a nephrologist when indicated. Red = as for orange but prepare for renal replacement if eGFR less than 30 mL/min/1.73 m².

Reproduced with permission from Kidney Health Australia.¹⁹

Abbreviations: ACR = albumin to creatinine ratio; GFR = glomerular filtration rate.

on biopsy, including advanced tubular, interstitial and vascular damage. These more heterogeneous changes are particularly common in patients with nonclassical DKD. This suggests that the effects of age, blood pressure and intrarenal vascular disease may be causing decreased eGFR independent of the presence of albuminuria.^{16,17}

Nondiabetic kidney disease in patients with diabetes

Kidney disease in a patient with diabetes may not always be due to diabetes. The presence of the following factors should alert the clinician to the possibility of other aetiologies: absence of retinopathy, diabetes of less than five years' duration, acute kidney injury rather than gradual progression towards CKD, presence of haematuria or another systemic disease and presence of the nephrotic syndrome (albuminuria more than 3 g per 24 hours, low serum albumin, oedema). Among these factors, the absence of retinopathy and short duration of diabetes are the strongest predictors of nondiabetic kidney disease.¹⁸

If a nondiabetic aetiology is suspected, it is essential to exclude reversible causes of kidney disease. Investigations may include renal tract ultrasound, measurement of serum autoantibodies or immunoglobulins and particularly renal biopsy if the patient does not fit the usual presentation.

Classifying diabetic kidney disease

Although microalbuminuria can potentially be a useful marker of progressive DKD, the limitations of microalbuminuria in this context need to be appreciated, as outlined above. It is therefore

still recommended that patients with diabetes be tested for albuminuria. Albuminuria is ideally measured by immunoassay of an early morning, first pass urine sample. It should also be appreciated that the urinary albumin to creatinine ratio (ACR) has an individual coefficient of variation of 30 to 40%. Therefore, at least two, and preferably three, measurements should be performed before making a diagnosis of microalbuminuria. Albuminuria may also fluctuate with factors that have no causal relation to the development of nephropathy (e.g. concurrent urinary tract infections, exercise, drugs, weight fluctuations, febrile illness and dietary modifications).

The combined contributions of albuminuria, measured as ACR, and eGFR to the prognosis of patients with DKD are reflected by the development of a two-dimensional composite ranking system based on renal and cardiovascular risk (Figure).¹⁹ Most guidelines now actively discourage use of the term 'microalbuminuria' and instead suggest assigning albuminuria to three categories:

- A1 = normal to mildly elevated risk of adverse outcomes related to CKD
- A2 = moderately increased risk of adverse outcomes related to CKD ('A2' used instead of 'microalbuminuria')
- A3 = severely increased risk of adverse outcomes related to CKD ('A3' used instead of 'macroalbuminuria' or 'proteinuria').

CKD is divided into five kidney function stages based on eGFR, with a subdivision of stages 3 into stages 3a and 3b to reflect the increased risk for cardiovascular disease that has been reported when eGFR drops below 45 mL/min/1.73 m².

Treatment of diabetic kidney disease

The aim of treatment of patients with classical and nonclassical DKD is to limit the speed and extent of progression of the disease. GPs have a crucial role in this pursuit via active monitoring and treatment of hyperglycaemia, hypertension and hyperlipidaemia. Targets for treatment need to be tailored for each individual patient, taking into account age, burden of comorbidities, life expectancy and current pharmacotherapy.²⁰

Intensive glycaemic control (HbA_{1c} less than 7% [less than 53 mmol/mol]) delays the development and progression of microalbuminuria and reduces the risk of developing other microvascular complications in both patients with type 1 and type 2 diabetes. Although there is good evidence to suggest that elevated glucose levels initiate and promote early DKD and that interventions to improve glucose control can slow progression of albuminuria, it is only recently that evidence has emerged to demonstrate that good glycaemic control slows the rate of GFR decline and retards progression to ESKD.^{8,11,12}

However, evidence from recent trials in both patients with type 1 and type 2 diabetes suggest that aiming for an HbA_{1c} of less than 7% (less than 53 mmol/mol) is associated with a risk of severe hypoglycaemia and increased all-cause mortality. This risk is greatest in those with pre-existent cardiovascular disease, long-standing diabetes and a history of poor glycaemic control. With this in mind, individualisation of HbA_{1c} targets has been proposed, depending on the stage of disease and glycaemic control. The suggested target HbA_{1c} for patients with early diabetes is less than 7% (53 mmol/mol), but relaxed to less than 8% (64 mmol/mol) for those with longstanding poor glycaemic control.²⁰ It may also be appropriate to consider relaxing glycaemic targets in patients with established DKD (eGFR less than 60 mL/min/1.73 m²) due to the risk of hypoglycaemia with reduced renal clearance of insulin and many oral hypoglycaemic agents.

Moderate blood pressure control (systolic blood pressure 120 to 140 mmHg) is associated with decreased adverse renal-related outcomes and increased overall patient survival. However, aggressive control of systolic blood pressure to less than 120 mmHg may be associated with an increase in all-cause mortality. This risk is particularly relevant to high-risk patients such as those with longstanding diabetes and pre-existing cardiovascular disease: in these patients the blood pressure target is less than 140/90 mmHg. Stricter blood pressure control (less than 120 to 130/80 mmHg) may be appropriate in younger patients, provided these targets can be achieved without side effects of treatment.²¹

ACE inhibitors or angiotensin II receptor blockers (ARBs) are recommended as first-line therapy for patients with diabetes and either hypertension or albuminuria or both. ACE inhibitors or ARBs slow the progression from normoalbuminuria to microalbuminuria in patients with hypertension; however, it remains controversial as to whether this effect is independent of improved blood pressure control. ACE inhibitors or ARBs are generally

recommended in normotensive albuminuric patients with microalbuminuria, although it is not clear whether ACE inhibitors or ARBs offer an additional benefit over other classes of antihypertensives. There is no evidence to support the use of a RAA blocker for primary prevention of DKD in normotensive normoalbuminuric patients with diabetes. The combination of an ACE inhibitor and an ARB does not offer any additional cardiovascular or renal protection and may be harmful, in particular increasing the patient's risk for acute kidney injury and hyperkalaemia.²¹

The benefit of lipid-lowering therapy is proportional to underlying cardiovascular risk, with a 9% relative risk reduction in all-cause mortality per mmol/L reduction in low-density lipoprotein (LDL) cholesterol level. Therefore, patients with the highest cardiovascular risk have the most to gain from improved lipid control and should be treated the most aggressively. There are no specific lipid targets for patients with diabetes and CKD. However, these are encouraged to achieve the general lipid goals of a total cholesterol level of less than 4.0 mmol/L, a LDL-cholesterol level of less than 2.0 mmol/L, a high-density lipoprotein cholesterol level of 1.0 mmol/L or more and a triglyceride level of less than 2.0 mmol/L, as recommended by the RACGP and Diabetes Australia *General Management of Type 2 Diabetes* guidelines.²² Of note, under current guidelines for the Pharmaceutical Benefits Scheme (PBS), patients with diabetes and microalbuminuria can be prescribed a lipid-lowering therapy at any cholesterol level. Low GFR without albuminuria is currently not recognised by the PBS as a high-risk cardiovascular category. There is no firm evidence to suggest that statin therapy and reduction of LDL-cholesterol level results in preservation of GFR. There is only limited evidence to support the use of statin therapy in patients on dialysis from the cardiovascular risk reduction perspective. A reasonable approach is to continue statin therapy if the patient is already taking it, but not to commence a statin de novo after commencing dialysis.

Conclusion

Screening people with diabetes for early markers of DKD and initiating measures to retard the progression of kidney disease are part of routine clinical practice. In addition, it is necessary to measure, assess and manage cardiovascular risk factors aggressively. Attention to glycaemic, lipid and blood pressure control as part of a multifactorial, target-driven approach still remains the cornerstone of the management of patients with DKD. There is an increasing recognition of the discordance between albuminuria and GFR in patients with this kidney disease. The finding of elevated levels of albuminuria does not always predict GFR loss and conversely, GFR can decline without an increase in albuminuria in people with diabetes. **MT**

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A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

COMPETING INTERESTS: None.

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