Renal disease in diabetes: when to investigate for causes other than diabetes

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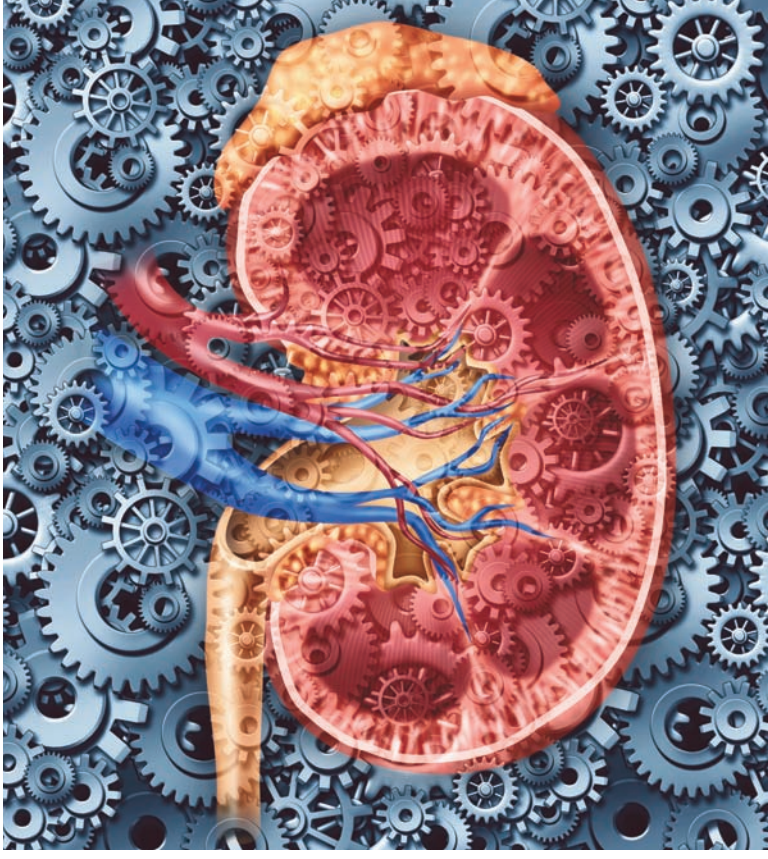
In patients with type 1 or type 2 diabetes and chronic kidney disease, a careful assessment is needed to identify nondiabetic kidney disease because some forms of this condition are treatable and remission is possible.



Key points

- **The spectrum of diabetic kidney disease is much broader than the traditional proteinuric model described in the 1980s.**
- **Up to 30% of patients with chronic kidney disease and type 2 diabetes have been reported to have nondiabetic kidney disease (NDKD).**
- **It is important to identify such patients because some forms of NDKD are treatable, sometimes leading to remission.**
- **Patients with diabetes and reduced kidney function are at risk of contrast-induced nephropathy.**
- **Clues to support a diagnosis of NDKD include: early onset of proteinuria or a rapid decrease in glomerular filtration rate (GFR) with a short duration of diabetes; the presence of an active urine sediment; signs or symptoms of another systemic disease; the absence of retinopathy or a significant reduction in GFR after starting a renin-angiotensin system inhibiting agent; and small kidneys on an ultrasonogram.**

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End-stage kidney disease secondary to diabetes is the most common reason why renal replacement therapy is started. The pathological changes of classic diabetic nephropathy, which are predominantly glomerular, are usually reported to be irreversible and there is no specific therapy for established (proteinuric) diabetic nephropathy. Despite attention to strict metabolic control and use of renin-angiotensin system (RAS) inhibiting agents, patients with established diabetic nephropathy have a poor prognosis.

Current dogma suggests that it is only possibly to delay the development of end-stage kidney disease in patients with established diabetic nephropathy by less than two years. However, the diagnosis of kidney disease in people with diabetes is almost always made clinically and it is possible that some patients with diabetes have other causes of proteinuric chronic kidney disease (CKD) apart from diabetes. It is important to identify such patients because, in contrast to diabetic nephropathy, some forms of nondiabetic kidney disease (NDKD) are treatable and remission is possible if the correct treatment is prescribed.[1]

Biopsy-proven NDKD in type 1 diabetes is rare (<5%), but up to 30% of patients with type 2 diabetes and proteinuric CKD have been reported to have NDKD. However, it is difficult to ascertain the exact prevalence of NDKD as reported rates may reflect a clinical bias in the selection of patients for renal biopsy and vary according to the ethnic group studied.[2]

Spectrum of CKD in diabetes

When considering a diagnosis of NDKD in people with diabetes, it is also important to appreciate that the spectrum of clinical presentations for patients with CKD and diabetes is much broader than the traditional proteinuria-centred model that was formulated in the 1980s. There is now an increased awareness that some patients with

diabetes, usually elderly women with type 2 diabetes, can have a reduced glomerular filtration rate (GFR) while remaining normoalbuminuric; however, it is unusual for such patients to progress to end-stage kidney disease without making the transition to proteinuria.[3]

This phenomenon is not entirely accounted for by the use of RAS inhibiting agents, which can mask an increase in albuminuria level. Putative aetiologies of renal impairment in this setting include hyperglycaemia, ageing, hypertension and vascular disease. We would recommend that most patients with diabetes and normoalbuminuric renal impairment do not need extensive investigation for other renal disorders unless there is an unexpected and significant reduction (>25%) in GFR over a relatively short period of time. For patients with diabetes and renal disease, referral to a nephrologist is recommended if the clinical features listed in the box to the right are present.

It is timely that the contemporary approach to staging renal disease in people with and without diabetes is now based on both the level of urinary albumin excretion and GFR, as shown in the Table.[4] This classification approach recognises the graded independent but additive relationship between increasing albuminuria and reduced estimated GFR with adverse outcomes.[4]

This new classification system and an awareness of the widening spectrum of CKD presentations in people with diabetes have promoted use of the term diabetic kidney disease (DKD). The term diabetic nephropathy should be reserved for patients with diabetes and persistent clinically detectable proteinuria that is associated with an elevation in blood pressure and a decline in GFR. However, subclinical proteinuria, termed microalbuminuria, has been recognised as a definable early stage in the natural history of rising albuminuria levels in DKD and is sometimes termed 'incipient diabetic nephropathy'.

Criteria for referral of patients with diabetes and chronic kidney disease to a nephrologist

- eGFR of less than 30 mL/min/1.73 m^2
- Persistent significant albuminuria (ACR ≥30 mg/mmol)
- A consistent decline in eGFR from a baseline value of <60 mL/min/1.73 m^2 (a decline >5 mL/min/1.73 m^2 over a six-month period confirmed on at least three separate readings)
- Glomerular haematuria with macroalbuminuria
- CKD and hypertension that is hard to get to target despite use of at least three antihypertensive medications

Note: The patients wishes and comorbidities should be taken into account when considering referral.

Abbreviations: ACR = albumin:creatinine ratio; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

What are the causes of NDKD?

A variety of renal lesions have been reported to occur in patients with diabetes and include immunoglobulin A nephropathy, membranous nephropathy, membranoproliferative glomerulonephritis, hypertensive renal disease, and focal and segmental glomerulosclerosis. These lesions can be either independent of, or superimposed on, diabetic nephropathy.

Focal segmental glomerulosclerosis is likely to be the most common form of NDKD in people with type 2 diabetes. It has also been reported to be associated with morbid obesity. In a recent study of NDKD in chinese patients with type 2 diabetes, proteinuria and a GFR of less than 60 mL/min/1.73 m^2, the frequencies of the various forms of NDKD detected on biopsy were:

- focal segmental glomerulosclerosis – 37.7%
- immunoglobulin A nephropathy – 16%

Table. Classification of chronic kidney disease*[4]

Kidney function stage	GFR (mL/min/1.73 m^2)	Albuminuria stage		
		Normal (urine ACR mg/mmol) Men <2.5 Women <3.5	Microalbuminuria (urine ACR mg/mmol) Men 2.5–25 Women 3.5–35	Macroalbuminuria (urine ACR mg/mmol) Men >25 Women >35
1	>90	Not CKD unless haematuria or structural or pathological abnormalities present		
2	60–89			
3a	45–59			
3b	30–44			
4	15–29			
5	<15 on dialysis			

* Refer to colour-coded action plans for management strategies in *Chronic Kidney Disease (CKD) Management in General Practice (2nd edition).* See: http://www.kidney.org.au/HealthProfessionals/ tabid/582/Default.aspx.

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Abbreviations: ACR = albumin:creatinine ratio; CKD = chronic kidney disease; GFR = glomerular filtration rate.

- minimal change disease – 16%
- glomerulosclerosis – 12%
- mesangial proliferative glomerulonephritis – 10%
- membranous nephropathy – 9%.[5]

The frequencies of various forms of NDKD vary according to the ethnic population studied and the indications for renal biopsy at different centres. In Indigenous Australians with diabetes and proteinuria, the existence of focal segmental glomerulosclerosis or postinfectious glomerulonephritis should be considered.[6]

When to suspect NDKD

Clues that support a diagnosis apart from diabetes as the predominant aetiological factor for the development of CKD are shown in the box on this page.

Proteinuric DKD usually takes at least 10 years to develop in people with type 1 diabetes. The onset of proteinuria that is less than five years from the onset of type 1 diabetes would be suggestive of another disease process. In people with type 2 diabetes, there is usually a latent period of hyperglycaemia before diabetes is diagnosed and it is therefore not uncommon for patients to present with at least microalbuminuria. Hence, it is possible for diabetic nephropathy to develop during a shorter time interval after the diagnosis of type 2 compared with type 1 diabetes. The presence of an active urinary sediment containing red cells and cellular casts would suggest another disease process.[7] The presence of proliferative retinopathy has recently been shown to be a highly specific indicator for diabetic nephropathy.[8]

Indications for considering a kidney biopsy in a patient with diabetes and CKD include the onset of proteinuria soon after the diagnosis of diabetes, rapidly increasing proteinuria or nephrotic range proteinuria, evidence of other systemic disease processes or the presence of an active urinary sediment.

A reduction in GFR after commencement of a RAS inhibiting agent is an expected finding due to a decrease in intraglomerular pressure. This has been associated with better renal outcomes in patients with established diabetic nephropathy. However, a greater than 25% drop in GFR two to four weeks after commencement of an ACE inhibitor or an angiotensin receptor blocker should prompt consideration of renal artery stenosis, especially in the setting of refractory hypertension.[4]

The finding of enlarged kidneys on imaging would favour diabetes as the underlying cause for CKD. The presence of other systemic diseases, such as systemic lupus erythematosus, human immunodeficiency virus infection or liver disease, should raise concerns about glomerular disease apart from diabetes.[7]

The concurrent finding of retinopathy and CKD would support diabetes as being the underlying cause of CKD in people with diabetes. However, the absence of retinopathy, especially in type 2 diabetes, although increasing the likelihood of NDKD, does not exclude a finding of the classic structural changes of diabetic nephropathy. A Danish study of 51 consecutive patients with type 2 diabetes and proteinuria without any evidence of retinopathy found that 35 (69%) had classic diabetic glomerulopathy on biopsy. For the remaining 16 patients, near normal renal structure was found in nine and various forms of glomerulonephritis was found in seven.[9]

Likelihood of nondiabetic kidney disease in people with diabetes

Likely

- Onset of proteinuria soon after the diagnosis of diabetes
- Rapid increase in proteinuria/nephrotic range proteinuria
- Signs or symptoms of another systemic disease
- Presence of active urinary sediment
- Greater than expected reduction in GFR (>25%) with use of renin-angiotensin system inhibiting agents
- Refractory hypertension
- Absence of retinopathy
- Small kidneys on ultrasonogram

Unlikely

- Persistent and steadily progressive albuminuria/proteinuria
- Normal to large kidneys on ultrasound
- Presence of proliferative retinopathy
- No history of contrast-induced nephropathy

Contrast-induced nephropathy in patients with diabetes and CKD

Patients with diabetes and reduced kidney function are at a higher risk of contrast-induced nephropathy than patients without diabetes and reduced kidney function. In a prospective study in patients with a baseline serum creatinine level of more than 150 µmol/L who had a CT scan with contrast, those with diabetes had a higher incidence of contrast-induced nephropathy than those without diabetes (8.8% *vs* 4.0%, respectively).[10]

Although contrast-induced nephropathy usually only results in a transient increase in serum creatinine level, with a decline in creatinine level occurring three to seven days after the administration of radiocontrast, it is becoming increasingly appreciated that even after recovery from an episode of acute kidney injury there is still an increased risk of CKD progression. A recent study has shown that in patients with diabetes, any acute kidney injury episode versus no episodes was associated with an increased risk of progression to a GFR of less than 30 mL/min/1.73 m^2 over a five-year follow-up period, independent of other major risk factors of progression (hazard ratio 3.56, 95% confidence interval, 2.76–4.61).[11]

The optimal therapy to prevent contrast-induced nephropathy remains uncertain. However, intravenous hydration with normal saline, the avoidance of NSAIDs, the use of acetylcysteine and sodium bicarbonate, and the administration of nonionic contrast agents should be considered in patients with diabetes before the

administration of radiocontrast media to reduce the chances of developing acute kidney injury.[12]

For patients with diabetes and reduced renal function, guidelines recommend withholding metformin for 48 hours from the time of a radiocontrast study with a re-evaluation of renal function before restarting metformin.[13] This applies to patients with an estimated GFR ranging from 60 to 30 mL/min/1.73 m^2 because the use of metformin is contraindicated if estimated GFR is less than 30 mL/min/1.73 m^2.[14] It is also worth noting that most of the new glucose-lowering medications that target the incretin effect, such as exenatide, liraglutide and the dipeptidyl peptidase-4 inhibitors (except linagliptin), are not indicated for patients with an estimated GFR of less then 30 mL/min/1.73 m^2 and require a dose reduction in the setting of renal impairment.

Conclusion

Evaluation of patients with atypical features of DKD should include careful assessment of the clinical presentation. In the absence of another identifiable and treatable cause of kidney disease, patients with diabetes and CKD should be treated as if they have DKD. **ET**

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References

1. Chang TI, Park JT, Kim JK, et al. Renal outcomes in patients with type 2 diabetes with or without coexisting non-diabetic renal disease. Diabetes Res Clin Pract 2011; 92: 198-204.
2. Kumar J, Sahai G. Non-diabetic renal disease in diabetes. Clinical queries. Nephrology 2012; 102: 172-177.
3. Macisaac RJ, Jerums G. Diabetic kidney disease with and without albuminuria. Curr Opin Nephrol Hypertens 2011; 20: 246-257.
4. Chronic Kidney Disease (CKD) Management in General Practice (2nd edition). Melbourne: Kidney Health Australia, 2012.
5. Mou S, Wang Q, Liu J, et al. Prevalence of non-diabetic renal disease in patients with type 2 diabetes. Diabetes Res Clin Pract 2010; 87: 354-359.
6. Hoy WE, Samuel T, Mott SA, et al. Renal biopsy findings among Indigenous Australians: a nationwide review. Kidney Int 2012; 82: 1321-1331.
7. National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQI). KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease, 2013. Available online at: www.kdoqi.org (accessed June 2013).
8. He F, Xia X, Wu XF, Yu XQ, Huang FX. Diabetic retinopathy in predicting diabetic nephropathy in patients with type 2 diabetes and renal disease: a meta-analysis. Diabetologia 2013; 56: 457-466.
9. Christensen PK, Larsen S, Horn T, Olsen S, Parving HH. Causes of albuminuria in patients with type 2 diabetes without diabetic retinopathy. Kidney Int 2000; 58: 1719-1731.
10. Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. N Engl J Med 1989; 19; 320: 143-149.
11. Thakar CV, Christianson A, Himmelfarb J, Leonard AC. Acute kidney injury episodes and chronic kidney disease risk in diabetes mellitus. Clin J Am Soc Nephrol 2011; 6: 2567-2572.
12. Consensus Guidelines for the prevention of contrast induced nephropathy. Canadian Association of Radiologists, 2013. Available online at: www.car.ca (accessed June 2013).
13. The Royal Australian and New Zealand College of Radiologists (RANZCR). Guidelines for iodinated contrast administration. RANZCR, 2009.
14. Diabetes management in general practice: guidelines for type 2 diabetes (2011/12). 17th edition. Diabetes Australia and RACGP, 2011. Available online at: http://www.racgp.org.au/your-practice/guidelines/diabetes/ (accessed June 2013).