Diagnosis of diabetic kidney disease: state of the art and future perspective

Frederik Persson[1] and Peter Rossing[1,2]

[1]Steno Diabetes Center Copenhagen, Gentofte, Denmark; and [2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Approximately 20% to 40% of patients with type 1 or type 2 diabetes mellitus develop diabetic kidney disease. This is a clinical syndrome characterized by persistent albuminuria (> 300 mg/24 h, or > 300 mg/g creatinine), a relentless decline in glomerular filtration rate (GFR), raised arterial blood pressure, and enhanced cardiovascular morbidity and mortality. There is a characteristic histopathology. In classical diabetic nephropathy, the first clinical sign is moderately increased urine albumin excretion (microalbuminuria: 30–300 mg/24 h, or 30–300 mg/g creatinine; albuminuria grade A2). Untreated microalbuminuria will gradually worsen, reaching clinical proteinuria or severely increased albuminuria (albuminuria grade A3) over 5 to 15 years. The GFR then begins to decline, and without treatment, end-stage renal failure is likely to result in 5 to 7 years. Although albuminuria is the first sign of diabetic nephropathy, the first symptom is usually peripheral edema, which occurs at a very late stage. Regular, systematic screening for diabetic kidney disease is needed in order to identify patients at risk of or with presymptomatic diabetic kidney disease. Annual monitoring of urinary albumin-to-creatinine ratio, estimated GFR, and blood pressure is recommended. Several new biomarkers or profiles of biomarkers have been investigated to improve prognostic and diagnostic precision, but none have yet been implemented in routine clinical care. In the future such techniques may pave the way for personalized treatment.

Kidney International Supplements (2018) **8,** 2–7; https://doi.org/10.1016/j.kisu.2017.10.003

KEYWORDS: albuminuria; biomarker; diabetic kidney disease; diabetic nephropathy; glomerular filtration rate

Correspondence: *Peter Rossing, Steno Diabetes Center Copenhagen, Niels Steensens Vej 2, 2820 Gentofte, Denmark. E-mail: Peter.Rossing@regionh.dk*

Diabetic kidney disease is a major cause of morbidity and mortality in diabetes. Indeed, the excess mortality of diabetes occurs mainly in individuals with diabetes and proteinuria, and results not only from end-stage renal disease (ESRD) but also from cardiovascular disease, with the latter being particularly common in patients with type 2 diabetes.[1–3] Clinically, diabetic kidney disease is characterized by progressive kidney damage reflected by increasing albuminuria, impairment in renal function (decline in glomerular filtration rate [GFR]), elevated blood pressure, and excess morbidity and mortality due to cardiovascular complications. Diabetic kidney disease rarely develops in patients with type 1 diabetes before 10 years following diagnosis, whereas approximately 3% of patients with newly diagnosed type 2 diabetes already have overt nephropathy.[4] Diabetic kidney disease is the single most common cause of ESRD in many parts of the world including Europe, Japan, and the USA, and patients with diabetes account for 25% to 45% of all patients enrolled in ESRD programs.[5]

Because not all individuals with diabetes develop all the possible complications of the condition, systematic screening for relevant complications has become a major part of diabetes care today. The early detection of complications allows for more focused preventive treatment, or specific treatment to delay progression of a complication in its early stages. The main focus of treatment for diabetes is preventive: in essence, the aim of reducing blood glucose levels and maintaining glucose control is to prevent classical micro- and macrovascular complications.

Screening, diagnosis, and treatment for diabetic kidney disease have advanced substantially over the last 3 decades, improving both time to diagnosis and life-years gained after diagnosis.[6,7] To further this progress, current research seeks to develop new methods for the early detection of diabetic kidney disease, as well as improved treatment.

Definition of diabetic kidney disease

Diabetic kidney disease (also termed "chronic kidney disease" [CKD] due to diabetes or diabetic nephropathy) is defined in both type 1 and type 2 diabetes as the presence of persisting severely elevated albuminuria of >300 mg/24 h (or >200 μg/min), or an albumin-to-creatinine ratio (ACR) of >300 mg/g, confirmed in at least 2 of 3 samples, with concurrent presence of diabetic retinopathy and absence of signs of other forms of renal disease.[8] As such, this clinical diagnosis requires only basic clinical and laboratory evaluations. The

normal range for albuminuria is <30 mg/g, and the abnormal range is >30 mg/g, but values within both these ranges may be associated with an elevated risk of renal and cardiovascular disease.[9] The presence of moderately elevated urine albumin excretion (microalbuminuria) (30–300 mg/g) is widely regarded as a precursor of diabetic nephropathy, both indicating early risk and providing a target for intervention. However, in some cases microalbuminuria can display remission, either spontaneously or owing to treatment,[10–12] resulting in a lower renal risk compared with progression of albuminuria.

The broader term "kidney disease in diabetes" is used for patients with CKD (impaired renal function: estimated GFR [eGFR] < 60 ml/min per 1.73 m^2 or proteinuria) regardless of the background. Although impaired renal function with normal albuminuria (ACR < 30 mg/g) is prevalent, particularly in elderly individuals, it is much less likely to progress if albuminuria is not present.[13,14]

The Italian Renal Insufficiency and Cardiovascular Events (RIACE) study of more than 15,000 participants with type 2 diabetes suggested that those with elevated albuminuria displayed the typical microvascular complications, whereas nonalbuminuric individuals with impaired renal function had a more cardiovascular or macrovascular phenotype.[13]

For CKD in general, including in patients with diabetes, it has been recommended to stage the severity of the condition using a combination of etiology (if known), level of urinary albumin excretion, and eGFR category (Figure 1).[15] The National Kidney Foundation Kidney Disease: Outcomes Quality Initiative (KDOQI) working group for diabetes and CKD suggested that absence of retinopathy, fast deterioration of GFR, rapidly increasing or nephrotic-range albuminuria (>2500 mg/g), active urinary sediments, refractory hypertension, or signs or symptoms of other systemic diseases should raise suspicion of nondiabetic causes of CKD.[16]

Pathology

If renal biopsies were feasible in all patients without safety considerations, many patients would probably be diagnosed with early stages of diabetic nephropathy. Morphological changes such as mesangial expansion and thickening of the glomerular and tubular basement membranes, as well as typical glomerulosclerosis with nodular mesangial lesions (Kimmelstiel-Wilson lesions), can be attributed to the impact of hyperglycemia and hyperfiltration. These changes may be observed after only a few years of disease, but their presence is variable, and patients with long-standing diabetes may display only minor changes. Because renal biopsy is not without risk of complications, the procedure is rarely used in routine clinical practice in uncomplicated cases, and is often reserved for cases with severe albuminuria, a fast decline in GFR, or where differential diagnoses are required.

Prevalence

The global Developing Education on Microalbuminuria for Awareness of Renal and Cardiovascular Risk in Diabetes

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m^2) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Figure 1 | Staging of CKD.[15] Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red: very high risk. Reprinted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3:1–150. Copyright © 2013 KDIGO. CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.