Diabetic Kidney Disease

3

Ting Cai and Junwei Yang

Abstract

Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease (ESRD) and is strongly associated with mortality in patients with diabetes. Persistent albuminuria is the hallmark of DKD, and some patients will finally develop ESRD with gradually decreased glomerular filtration rate (GFR) and increased serum creatinine concentration. Glomerular basement membrane thickening, mesangial expansion, mesangial matrix accumulation, Kimmelstiel–Wilson nodules, and tubulointerstitial fibrosis are typical pathological changes in DKD. Screening for DKD should begin at 5 years after the diagnosis of type 1 diabetes and at the diagnosis of type 2 diabetes, which should include measurement of urinary albumin-to-creatinine ratio and serum creatinine concentration, estimation of GFR, and ophthalmologic examination. The progression of DKD may be slowed by optimal therapeutic approaches, including lifestyle improvement, strict glycemic and blood pressure control, control of dyslipidemia, and renin–angiotensin–aldosterone system blockade. Patients who develop ESRD require renal replacement therapy.

3.1 Introduction

Diabetes mellitus, a disease no longer associated with affluence, is on the rise across the world. More than 425 million individuals currently have diabetes, and this number may increase to 693 million by 2045 if nothing is done [1]. The incidence of diabetic kidney disease (DKD) has more than doubled in the past decade, largely because of the increasing prevalence of type 2 diabetes. As a potential devastating complication of diabetes, DKD is currently the primary cause of end-stage renal disease (ESRD) and is the single strongest predictor of mortality in patients with diabetes that globally imposes an increased social and economic burden [2].

3.2 Natural Course of DKD

In the conventional course of DKD, pathological changes develop progressively over a long clinical silent period without evidence of proteinuria, impaired glomerular filtration rate (GFR), or hypertension. An increase in GFR, or hyperfiltration, is one of the earliest changes which is

T. Cai
Nanjing Medical University, Nanjing, Jiangsu, China

J. Yang (✉)
Centre for Kidney Disease, Second Affiliated Hospital, Nanjing Medical University, Nanjing, Jiangsu, China
e-mail: jwyang@njmu.edu.cn

J. Yang, W. He (eds.), *Chronic Kidney Disease*, https://doi.org/10.1007/978-981-32-9131-7_3

Table 3.1 Urinary ACR is a diagnostic test for microalbuminuria and macroalbuminuria

Condition	Urinary ACR (mg/g)	Terms
Normoalbuminuria	<30	Normally to mildly increased
Microalbuminuria	30–300	Moderately increased
Macroalbuminuria/ overt proteinuria	>300	Severely increased

ACR albumin-to-creatinine ratio

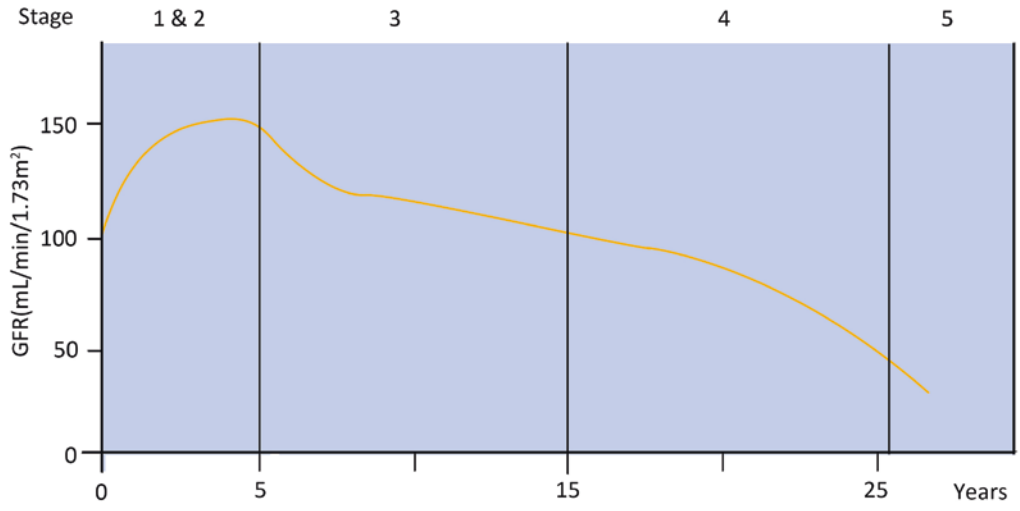
observed in most patients with type 1 diabetes and many with type 2 diabetes. Hyperfiltration is accompanied by renal hypertrophy, an increase in renal size. The next observable clinical manifestation is the development of microalbuminuria. A urinary albumin-to-creatinine ratio (ACR) between 0 and 30 mg/g and between 30 and 300 mg/g is customarily referred to as normoalbuminuria and microalbuminuria, respectively (Table 3.1). Microalbuminuria is currently accepted as a reliable marker to detect DKD at an early stage. However, not all patients with microalbuminuria will develop overt proteinuria and reduced GFR. Caramori et al. reviewed a number of clinical trials and revealed that only 30–40% of patients with microalbuminuria will develop macroalbuminuria (also called overt proteinuria, defined as urinary ACR >300 mg/g) (Table 3.1) [3]. Patients with established microalbuminuria may have different outcomes: they may improve, stay the same for a long period, or progress to macroalbuminuria and worse renal function. Perkins et al. reported as high as 50% probability for microalbuminuria to regress to normal levels in patients with type 1 diabetes [4].

Proteinuria, first characterized by Kimmelstiel and Wilson in a pathological report, results from complex damage in the glomerular filtration barrier, including the endothelial cells, basement membrane, and podocytes [5]. Proteinuria not only is a marker of glomerular injury but also implicates tubular injury. The natural course of DKD, proposed by Mogensen, including changes in proteinuria and GFR, as well as stages of preventive treatment, is shown in Fig. 3.1 [6]. In patients with type 1 diabetes, the average time from diagnosis of diabetes to onset of proteinuria is 19 years; in contrast, it is shorter and variable in patients with type 2 diabetes, as the disease may have already been present for several years prior to the establishment of diagnosis. Renal function may loss progressively over several years in patients with type 1 diabetes without intervention. Despite advances in interventions that slow down the progression of DKD, the number of patients progressing to renal failure is still increasing, making diabetes the major cause of ESRD [2].

3.3 Renal Pathology in DKD

After the onset of diabetes, kidney weight and size keep increasing until the establishment of overt nephropathy. Glomerular basement membrane (GBM) thickening is the first change that can be measured. Mesangial expansion (Fig. 3.2) develops later due to increased matrix accumulation in the mesangial region [7]. When renal dysfunction occurs, increased mesangial expansion and marked GBM thickening can be observed. Diffuse mesangial expansion can be linked with nodular lesions containing areas of marked mesangial expansion forming large round fibrillar mesangial zones with palisading of mesangial nuclei around the nodules and compression of the associated glomerular capillaries (Kimmelstiel–Wilson nodules) (Fig. 3.3). The severity of glomerular damage is associated with GFR and albuminuria.

Renal tubules and interstitium may also undergo structural changes, particularly in the later stages of DKD. The thickening of the tubular basement membrane (Fig. 3.2) closely correlates with the thickening of the GBM. Tubulointerstitial fibrosis and tubular atrophy may be the best pathologic predictors of progressive loss of GFR, which are more universal in patients with type 2 diabetes. In fact, the renal pathologic change is heterogeneous in patients with type 2 diabetes; only a subset of patients with type 2 diabetes has typical diabetic glomerulopathy, whereas a considerable proportion has



Stage	Pre (1&2)	Incipient DKD (3)	Overt DKD (4)	ESRD (5)
Structural changes	Hypertrophy GBM thickening	GBM thickening Mesangial expansion	Mesangial nodules (Kimmelstiel-Wilson nodules)	Glomerular closure Fibrosis
GFR	Increased by 20–50%	Supranormal values, predicted to decline if untreated	Decline ~10 mL/ min /1.73 m^2 / year	<10 mL/min/1.73 m^2
Urinary protein	Normal or occasional microalbuminuria	Microalbuminuria	Nephrotic proteinuria (>3.5 g /24h)	Often decline due to nephron loss
BP	Normal	Hypertension	Hypertension	Hypertension

Fig. 3.1 Nature course of diabetic kidney disease. *GFR* glomerular filtration rate; *DKD* diabetic kidney disease; *GBM* glomerular basement membrane; *BP* blood pressure

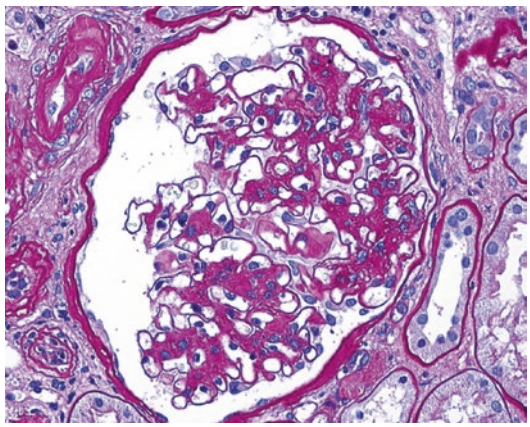


Fig. 3.2 Histopathological manifestations in diabetic kidney disease. Mesangial expansion and mesangial matrix accumulation are presented. (periodic acid-Schiff staining, ×400)

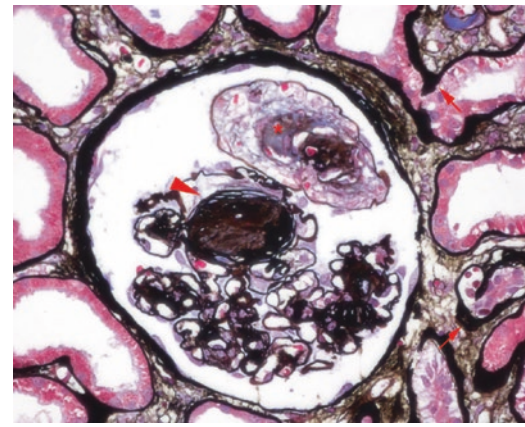


Fig. 3.3 Histopathological manifestations in diabetic kidney disease. Typical Kimmelstiel-Wilson nodule (arrowhead), dissolve of mesangium (star) and thickening of TBM (arrow) are presented. (methenamine silver staining, ×400)

more advanced tubulointerstitial and vascular damage [8]. Furthermore, the appearance of the kidney in some patients with type 2 diabetes is more suggestive of glomerular ischemia or tubulointerstitial disease.

3.4 Diagnosis of DKD

The main basis of the diagnosis of DKD is the test values of urinary protein excretion and estimated GFR (eGFR). Renal injury may be considered to be caused by diabetes in most patients with diabetes who have any of the following features [9]:

- Macroalbuminuria
- Diabetic retinopathy accompanied with microalbuminuria
- Microalbuminuria in patients diagnosed with type 1 diabetes for more than 10 years

Screening for DKD should begin at 5 years after the diagnosis of type 1 diabetes and at the diagnosis of type 2 diabetes. Patients with diabetes may annually undergo screening for DKD, which should include measurement of urinary ACR and serum creatinine concentration, estimation of GFR, and ophthalmologic examination (Fig. 3.4).

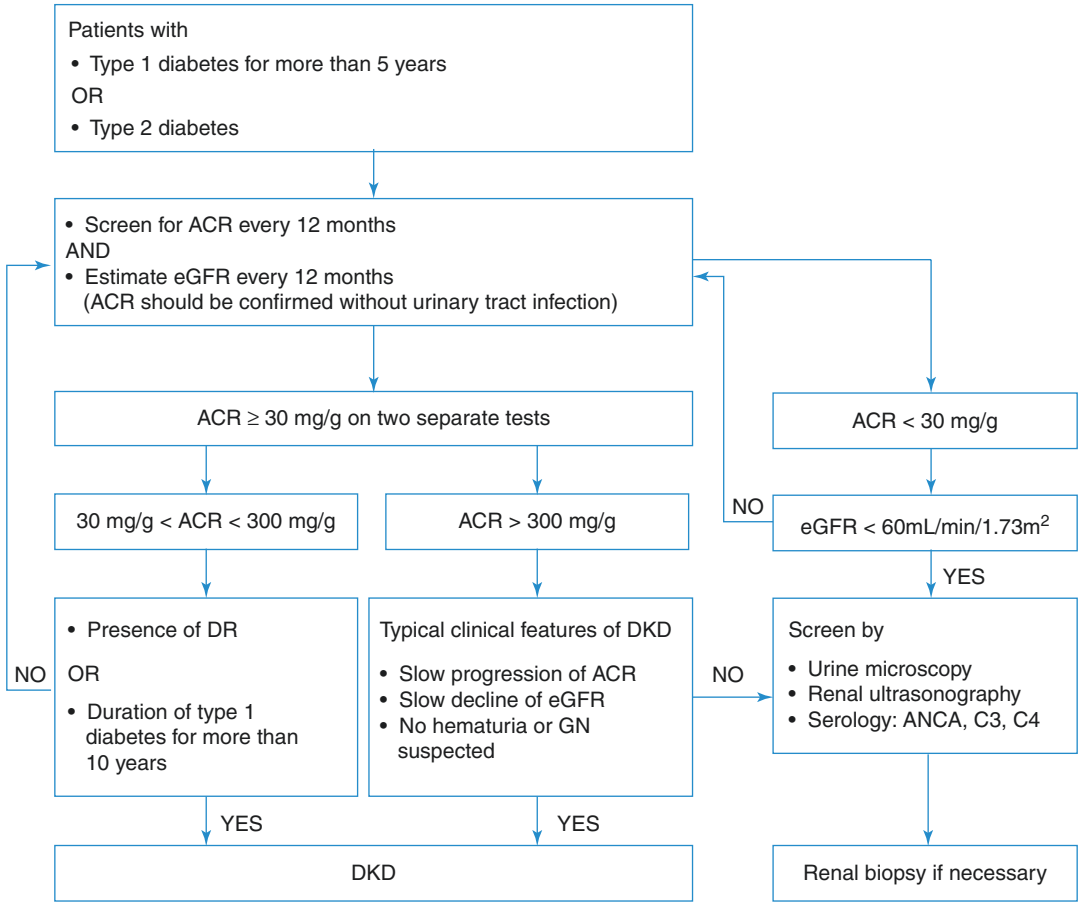


Fig. 3.4 Flowchart for the evaluation of DKD in patients with diabetes. *ACR* albumin-to-creatinine ratio; *eGFR* estimated glomerular filtration rate; *DR* diabetic retinopathy; *GN* glomerulonephritis; *DKD* diabetic kidney disease; *ANCA* anti-neutrophil cytoplasmic antibody; *C3* complement 3; *C4* complement 4

3.4.1 Measurement of Urinary ACR

Microalbuminuria is accepted as an independent risk factor associated with the progression of chronic kidney disease (CKD) and GFR loss. Measurement of microalbuminuria is currently widely available and easy to perform with relatively low cost. As the interpretation of results for albumin concentration alone may be unreliable due to variations in urinary concentration and timed collections are inconvenient, the ACR in a spot urine sample (preferably the first morning specimen) is recommended. Metabolic perturbation, hemodynamic factors, and presence of urinary tract infection may affect the appearance of albumin in the urine [10]. Hence, the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend that elevated ACR be confirmed in the absence of marked hypertension, urinary tract infection, and cardiac failure with two additional tests during the next 3–6 months [9].

3.4.2 Measurement of Serum Creatinine Concentration and eGFR

In clinical practice, the serum creatinine concentration is the most frequently used index to evaluate renal function. However, it is not sensitive enough and may be highly misleading when patients have low muscle mass, especially in elderly patients with diabetes. Therefore, the KDOQI guidelines recommend that the GFR be estimated with the Modification of Diet in Renal Disease Study equation; however, the evidence shows that the usefulness of eGFR alone as a regular screening test for CKD in diabetes is less secure [9].

3.4.3 Ophthalmologic Examination

A study including a cohort of patients with type 1 diabetes and with type 2 diabetes revealed that a large proportion of patients with type 1 diabetes and macroalbuminuria also showed signs of diabetic retinopathy, whereas nearly half of the patients with hypertension and type 2 diabetes who had macroalbuminuria did not have concomitant retinopathy [11]. Thus, the presence of retinopathy and macroalbuminuria in patients with type 1 diabetes strongly suggests DKD. In contrast, as for patients with type 2 diabetes, the accompanied presence of retinopathy is only partly useful in the discrimination of renal pathology, and the absence of retinopathy does not rule out the presence of DKD.

3.4.4 Indications for Renal Biopsy

Due to the variability in clinical course and complexity of clinical manifestation, renal biopsy is required for some patients with both diabetes and CKD to discriminate the potential cause of the kidney disease. Renal biopsy should be considered in the following patient situations:

1. eGFR rapidly declines, or renal dysfunction without significant proteinuria is observed.
2. The onset of proteinuria is sudden and progresses rapidly, particularly in patients with duration of type 1 diabetes <5 years. Alternatively, the evolution of proteinuria is atypical (e.g., nephrotic syndrome develops in the absence of persistent microalbuminuria).
3. The presence of macroscopic hematuria or active nephritic urinary sediment containing acanthocytes and red blood cell casts, which suggests glomerulonephritis, is detected.

3.5 Management of Patients with Diabetes and CKD

For patients with diabetes, when GFR <60 mL/min/1.73 m^2, complications of CKD should be evaluated, which commonly include electrolyte imbalance, metabolic acidosis, anemia, secondary hyperparathyroidism, and CKD–mineral bone disorder. Adjustment of drugs' dosage is necessary (Table 3.2).

Table 3.2 Management of patients with diabetes and CKD according to GFR

GFR (mL/min/1.73 m^2)	Recommendation
All patients with diabetes	Screen for serum creatinine, ACR, eGFR, and serum potassium every 12 months
45–60	Consideration of dose adjustment of drugs in use
	Screen for eGFR every 6 months
	Screen for serum electrolyte (Ca, P included), acid alkali balance, hemoglobin, and parathyroid hormone
	Evaluation of vitamin D
	Consideration of test for bone mineral density
	Nutritional consultation
	Referral to nephrologist when diabetes with non-DKD or the cause of CKD is unknown
30–44	Screen for eGFR every 3 months
	Screen for serum electrolyte (Ca, P included), acid alkali balance, hemoglobin, parathyroid hormone, albumin, and weight
	Consideration of dose adjustment of drugs in use
<30	Referral to nephrologist

GFR glomerular filtration rate; *ACR* urinary albumin-to-creatinine ratio; *eGFR* estimated glomerular filtration rate; *CKD* chronic kidney disease; *DKD* diabetic kidney disease

3.5.1 Treatment of DKD

Interventions deemed useful in preventing the progression of DKD include lifestyle improvement, strict glycemic and blood pressure (BP) control, control of dyslipidemia, and renin–angiotensin–aldosterone system (RAAS) blockade. Patients who develop ESRD may require renal replacement therapy (Fig. 3.4).

3.5.1.1 Lifestyle Improvement

The KDOQI guidelines recommend a dietary protein intake of 0.8 g/kg body weight per day for individuals with diabetes and stage 1–4 CKD [9]. For patients with diabetes on hemodialysis (HD), 1.3 g/kg weight per day is suggested. Smoking should immediately be stopped upon the diagnosis of diabetes.

3.5.1.2 Glycemic Control

Hyperglycemia is the primary cause of DKD. Strict glycemic control through insulin or islet cell transplantation improves hyperfiltration, hyperperfusion, and glomerular capillary hypertension and decreases urinary albumin excretion in experimental diabetic animals. Moreover, strict glycemic control slows the development and progression of DKD in patients with diabetes.

In the Diabetes Control and Complications Trial (DCCT), patients with type 1 diabetes who received intensive therapy (average hemoglobin A1c [HbA1c] level of 7.2%) showed a 39% lower risk of developing microalbuminuria when compared to patients who received conventional therapy (average HbA1c level of 9.1%) at 6.5-year follow-up. Furthermore, patients receiving intensive therapy showed a 54% reduction in progression from microalbuminuria to macroalbuminuria [12]. At the end of the DCCT, all patients in the previous two groups received intensive therapy, and nephropathy was evaluated based on urine specimens at 3 and 4 years after the original DCCT. The average HbA1c level was 8.2% in the previous conventional therapy group, and 7.9% in the previous intensive therapy arm. However, the intensive therapy group still has advantage over the former conventional therapy group with an 86% lower risk of new-onset albuminuria. More recently, data from the DCCT and Epidemiology of Diabetes Interventions and Complications (EDIC) study suggested a 50% reduction of the long-term risk of impaired GFR in patients undergoing intensive therapy as compared to their counterparts receiving conventional therapy [13].

A number of major studies have also reported a lower risk of DKD in patients with type 2 diabetes undergoing stricter glycemic control. As shown in the United Kingdom Prospective Diabetes Study (UKPDS), newly diagnosed patients with type 2 diabetes were randomly divided into intensive therapy (HbA1c level of 7.0%) treated with sulfonylurea or insulin and conventional therapy (HbA1c level of 7.9%) with diet alone [14]. The reduction in the risk of developing microalbuminuria over 9 years and of

progression from microalbuminuria to proteinuria was 24% and 42%, respectively, in the intensive therapy group. After study termination, patients were observed for another 10 years. Although the HbA1c level between the two groups was comparable within 1 year, lower risk of microvascular disease and myocardial infarction persisted. This phenomenon of prolonged beneficial effects on complications of diabetes achieved through strict glycemic control even being followed by less intensive glycemic control has been described as "metabolic memory" or "legacy effect."

Considering the impressive results from several major clinical trials, the American Diabetes Association (ADA) suggests an HbA1c level of <7% for all patients with diabetes in order to reduce their risk of developing DKD [15]. The target blood glucose level can be achieved through treatment with insulin, oral hypoglycemic drugs, or a combination of both. Insulin can be used at any stage of DKD. However, oral hypoglycemic drugs should be carefully used according to one's renal function (Table 3.3) [16]. The use of most first- and second-generation sulfonylureas should be avoided when the eGFR is ˂60 mL/min/1.73 m^2. Biguanides (metformin) should not be used if GFR is <30 mL/min/1.73 m^2 or the serum creatinine concentration is >1.5 mg/dL in men and >1.4 mg/dL in women. Thiazolidinediones can be safely used in patients with DKD.

3.5.1.3 BP Control

In patients with type 1 diabetes, microalbuminuria is typically prior to hypertension. Conversely, hypertension may have already been present in some patients with type 2 diabetes when microalbuminuria is detected [17]. The appropriate BP at which therapy should be started, and the target of BP are topics that are still under debate. Higher BP is associated with increasing albuminuria and higher risk of renal failure in diabetes. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure trial, patients with type 2 diabetes were assigned to receive either intensive treatment with a systolic BP goal of <120 mmHg or standard therapy aim-

Table 3.3 Dose adjustment of oral hypoglycemic drugs in patients with diabetes and CKD

Medication class and agents	CKD stages 3, 4, and 5
First-generation sulfonylureas	
• Acetohexamide	• Avoid using
• Tolazamide	• Avoid using
• Tolbutamide	• Avoid using
Second-generation sulfonylureas	
• Glipizide	• No dose adjustment
• Gliclazide	• No dose adjustment
• Glyburide	• Avoid using
• Glimepiride	• Start carefully with a dose of 1 mg daily
Meglitinides	
• Repaglinide • Nateglinide	• Start carefully at 0.5 mg with meals when GFR <30 mL/min/1.73 m^2 • Start carefully at 0.5 mg with meals when GFR <30 mL/min/1.73 m^2.
Biguanides	
• Metformin	• Avoid using if serum creatinine >1.5 mg/dL in men, or >1.4 mg/dL in women, suggested by the US FDA • Avoid using when GFR <30 mL/min/1.73 m^2, recommended by British National Formulary and the Japanese Society of Nephrology
Alpha-glucosidase inhibitors	
• Acarbose	• Avoid using when GFR <30 mL/min/1.73 m^2.
DPP-4 inhibitor	
• Sitagliptin	• GFR >50 mL/min/1.73 m^2: 100 mg daily
	• GFR 30–50 mL/min/1.73 m^2: 50 mg daily (1/2 of regular dose)
	• GFR <30 mL/min/1.73 m^2: 25 mg daily (1/4 of regular dose)
• Saxagliptin	• GFR >50 mL/min/1.73 m^2: 5 mg daily
	• GFR ≤50 mL/min/1.73 m^2: 2.5 mg daily
• Linagliptin	• No dose adjustment
• Vildagliptin	• GFR ≥50 mL/min/1.73 m^2: 50 mg twice daily
	• GFR <50 mL/min/1.73 m^2: 50 mg daily (1/2 of regular dose)

CKD chronic kidney disease; *FDA* Food and Drug Administration; *GFR* glomerular filtration rate; *DPP-4* dipeptidyl peptidase 4

ing for <140 mmHg [18]. However, no difference in the risk of major cardiovascular events was observed between the two groups. In a secondary analysis of the Irbesartan Diabetic Nephropathy Trial (IDNT), progressive systolic BP decline up to 120 mmHg was associated with increased renal survival, but with higher mortality [19]. Thus considering the detrimental effect of high BP on renal function and from a safety concern, the National Kidney Foundation (NKF) and ADA have recommended an optimal BP target of <130/80 mmHg for renal and cardiovascular benefit in patients with diabetes who have nephropathy. As for patients with diabetes and ACR <30 mg/g, a BP target of 140/90 mmHg or less is recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) and Eighth Joint National Committee guidelines.

Patients with BP >120/80 mmHg should be suggested on BP reduction through lifestyle changes, which consist of weight loss, decreased sodium intake, and increased physical excise, among others. Patients with confirmed BP >140/80 mmHg should initiate pharmacological therapy promptly to reach the optimal BP. Treatment of hypertension may require selection from several different classes of antihypertensive drugs, and combination therapy is recommended with special considerations for hypertensive patients with diabetes. Pharmacological therapy should include a RAAS blocker (either an angiotensin-converting enzyme inhibitor [ACEI] or an angiotensin receptor blocker [ARB]); in addition, it is recommended to titrate up to the maximum approved dose if tolerated. Diuretics, calcium channel blockers, and β-blockers can be used as additional therapy to achieve the BP target goal in patients already treated with a RAAS blocker or as alternative therapy in individuals with poor tolerance of these drugs.

3.5.1.4 RAAS Blockade

In patients with diabetes who have established DKD, RAAS blockade using ACEIs or ARBs confers preferential renoprotection independent of BP reduction. Several clinical trials investigating a series of progressive kidney diseases have shown the value of ACEIs in slowing disease progression. In the Collaborative Study Group trial, which evaluated the renoprotective properties of captopril among patients with type 1 diabetes, captopril decreased urinary albumin excretion and delayed the progression of kidney disease compared with the placebo, although no difference of the median BP was observed between the two groups [20]. Other randomized controlled trials have reported that reduction in proteinuria appears to delay the progression of kidney disease among patients with overt nephropathy.

For patients with type 2 diabetes, results from different clinical studies are less consistent and flawed, possibly due to smaller sample sizes and the use of surrogate outcomes. Furthermore, the protective property of decreasing urinary albumin excretion seems to be less significant in patients with type 2 diabetes and DKD. Long-term benefit achieved from ACEIs was best shown in a 7-year study which compared the effects of enalapril and placebo in normotensive patients with type 2 diabetes who had microalbuminuria. The study period covered 5 years for the comparison between ACEI and placebo, followed by another 2 years, at which period patients could choose either enalapril or placebo. Initial therapy with enalapril stabilized renal function and urinary albumin excretion and reduced the risk of nephropathy by 42%. Urinary albumin excretion increased among patients initially treated with enalapril after stopping ACEI therapy but decreased among those treated with placebo who chose enalapril therapy [21].

ARBs share many effects with ACEIs and have a superior safety property, which includes lower risk of cough, angioedema, and hyperkalemia. The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan trial (RENAAL) compared losartan with conventional antihypertensive therapy in patients with type 2 diabetes and DKD. Fewer patients treated with losartan attained the primary composite endpoint of doubling of serum creatinine concentration, ESRD, or death; moreover, proteinuria level was reduced with losartan [22]. In the IDNT, irbesartan also showed renoprotective properties as compared to the calcium channel

blocker or placebo [23]. Concerning the shared RAAS-inhibiting effects of ACEIs and ARBs, both are believed to be effective in the treatment of DKD.

3.5.1.5 Lipid-Lowering Therapy

Dyslipidemia is prevalent in patients with DKD. It can promote the development of DKD. In non-dialysis patients with type 2 diabetes and DKD, treatment with statins provides marked cardiovascular benefit. A recent meta-analysis suggested a slight positive effect of statins on albuminuria and renal function. The KDIGO Clinical Practice Guideline for Lipid Management in CKD recommends treatment with statins for adult patients with diabetes and CKD who are not treated using chronic dialysis.

3.5.1.6 Renal Replacement Therapy

Available renal replacement modalities for patients with diabetes who have GFR <15 mL/min/1.73 m^2, uncontrolled heart failure, or hyperkalemia include peritoneal dialysis (PD), HD, and renal transplantation. Patients with diabetes on HD have lower rate of hospitalization and infection but higher rate of intradialytic hypotension and cardiac death than those on PD. PD is a better option for those with sclerosed forearm vessels, which seems to have a higher survival rate than HD in patients with diabetes who have residual renal function, except for the very elderly, and facilitates BP control and prevention of heart failure owing to slow and sustained ultrafiltration [24, 25]. However, PD is less effective than HD, and patients on PD are prone to protein loss and obesity.

3.5.1.7 Emerging Therapies

Considering the complex pathophysiology of diabetes and DKD, a number of new therapeutic agents to prevent or treat DKD have been attempted.

- Sodium–Glucose Cotransporter (SGLT) 2 Inhibitor

  The kidney reabsorbs all filtered glucose through SGLT1 and SGLT2, with SGLT2 being responsible for most of this task. SGLT2 inhibitors reduce glucose reabsorption, thereby decreasing blood glucose levels, and are the only insulin-independent glucose-lowering drugs. Currently, empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin are approved by the FDA. In experimental diabetic mice, SGLT2 inhibitor was shown to decrease hyperfiltration independent of reduction in blood glucose level. In addition, SGLT2 inhibitor may reduce early kidney growth and inflammation by lowering the blood glucose level. In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME) study, patients with type 2 diabetes at high cardiovascular risk were assigned to receive placebo or empagliflozin at a target dose of 10 mg or 25 mg [26]. Compared with placebo, empagliflozin decreased the risk of new-onset of or worsening nephropathy by 39%. Also, patients who received empagliflozin had a lower rate of doubling of serum creatinine concentration, initiation of renal replacement therapy, and death due to kidney disease. In addition to the EMPA-REG OUTCOME study, several studies investigating the effects of SGLT2 inhibition on cardiovascular and kidney outcomes are underway, which will be issued in the next few years. The findings of these studies will complement those of the EMPA-REG OUTCOME study and help in further understanding the therapeutic potential and safety of SGLT2 inhibition.
- Bardoxolone Methyl

  Bardoxolone methyl is a synthetic compound derived from oleanolic acid, which activates the Keap1–Nrf2 pathway and regulates inflammation in the kidney. In the Bardoxolone Methyl Treatment: Renal Function in CKD/Type 2 Diabetes (BEAM) study, patients with CKD and diabetes were randomly assigned to receive either bardoxolone methyl or placebo for 52 weeks [27]. Bardoxolone methyl significantly increased the mean eGFR compared with placebo at 24 weeks. The improvement lasted for another 28 weeks. Adverse events, particularly muscle spasms, were more frequent in the bardoxo-

lone methyl group. The Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus: the Occurrence of Renal Events study was designed to confirm the findings of the BEAM study. Unfortunately the study was prematurely stopped owing to unacceptable high rates of cardiovascular events in patients treated with bardoxolone methyl at a median duration of 7 months, and no benefit was observed about the risk of ESRD [28].

The beneficial effects of an Nrf2 agonist called dh404, which is a derivative of bardoxolone methyl, via reduction in inflammation and oxidative stress but only at low doses have recently been shown in mice. This finding rekindles the interests on renoprotection via activation of the Nrf2 pathway in DKD.

Key Messages

- DKD is the leading cause of ESRD and is strongly associated with mortality in patients with diabetes.
- Persistent albuminuria is the hallmark of DKD, and some patients will finally develop ESRD with gradually decreased GFR and increased serum creatinine concentration.
- GBM thickening, mesangial expansion, mesangial matrix accumulation, Kimmelstiel–Wilson nodules, and tubulointerstitial fibrosis are typical pathological changes in DKD.
- Screening for DKD should begin at 5 years after the diagnosis of type 1 diabetes and at the diagnosis of type 2 diabetes. Patients with diabetes may annually undergo screening for DKD, which should include measurement of urinary ACR and serum creatinine concentration, estimation of GFR, and ophthalmologic examination.
- The progression of DKD may be slowed by optimal therapeutic approaches, such as lifestyle improvement, strict glycemic and BP control, control of dyslipidemia, and RAAS blockade. Patients who develop ESRD require renal replacement therapy.

References

1. IDF Diabetes Atlas. 8th ed. 2017.
2. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care. 2014;37(10):2864–83.
3. Caramori ML, Fioretto P, Mauer M. The need for early predictors of diabetic nephropathy risk: is albumin excretion rate sufficient? Diabetes. 2000;49(9):1399–408.
4. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. N Engl J Med. 2003;348(23):2285–93.
5. Kimmelstiel P, Wilson C. Intercapillary lesions in the glomeruli of the kidney. Am J Pathol. 1936;12(1):83–98.7.
6. Mogensen C. How to protect the kidney in diabetic patients: with special reference to IDDM. Diabetes. 1997;46(Supplement 2):S104–S11.
7. Osterby R, Gall MA, Schmitz A, Nielsen FS, Nyberg G, Parving HH. Glomerular structure and function in proteinuric type 2 (non-insulin-dependent) diabetic patients. Diabetologia. 1993;36(10):1064–70.
8. Musso C, Javor E, Cochran E, Balow JE, Gorden P. Spectrum of renal diseases associated with extreme forms of insulin resistance. Clin Am Soc Nephrol. 2006;1(4):616–22.
9. KDOQI. Clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis. 2007;49(2 Suppl 2):S12–154.
10. Redon J. Measurement of microalbuminuria—what the nephrologist should know. Nephrol Dial Transplant. 2006;21(3):573–6.
11. Wolf G, Muller N, Mandecka A, Muller UA. Association of diabetic retinopathy and renal function in patients with types 1 and 2 diabetes mellitus. Clin Nephrol. 2007;68(2):81–6.
12. The Diabetes Control and Complications (DCCT) Research Group. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. Kidney Int. 1995;47(6):1703–20.
13. Group DER, de Boer IH, Sun W, Cleary PA, Lachin JM, Molitch ME, et al. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. N Engl J Med. 2011;365(25):2366–76.
14. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837–53.
15. American Diabetes Association. Clinical Practice Recommendations 2001. Diabetes Care. 2001;24(Suppl 1):S1–133.
16. KDIGO. 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3(1):1–150.

17. Hypertension in Diabetes Study (HDS). I. Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardiovascular and diabetic complications. J Hypertens. 1993;11(3):309–17.
18. Group AS, Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1575–85.
19. Pohl MA, Blumenthal S, Cordonnier DJ, De Alvaro F, Deferrari G, Eisner G, et al. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: clinical implications and limitations. J Am Soc Nephrol. 2005;16(10):3027–37.
20. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The collaborative study group. N Engl J Med. 1993;329(20):1456–62.
21. Ravid M, Lang R, Rachmani R, Lishner M. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. A 7-year follow-up study. Arch Intern Med. 1996;156(3):286–9.
22. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861–9.
23. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345(12):851–6.
24. Heaf JG, Lokkegaard H, Madsen M. Initial survival advantage of peritoneal dialysis relative to haemodialysis. Nephrol Dial Transplant. 2002;17(1):112–7.
25. Winkelmayer WC, Glynn RJ, Mittleman MA, Levin R, Pliskin JS, Avorn J. Comparing mortality of elderly patients on hemodialysis versus peritoneal dialysis: a propensity score approach. J Am Soc Nephrol. 2002;13(9):2353–62.
26. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016;375(4):323–34.
27. Pergola PE, Raskin P, Toto RD, Meyer CJ, Huff JW, Grossman EB, et al. Bardoxolone methyl and kidney function in CKD with type 2 diabetes. N Engl J Med. 2011;365(4):327–36.
28. De Zeeuw D, Akizawa T, Audhya P, Bakris GL, Chin M, Christ-Schmidt H, et al. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. N Engl J Med. 2013;369(26):2492–503.