CHAPTER 9

DIABETIC NEPHROPATHY

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INTRODUCTION

Diabetes mellitus is the most common cause of the end-stage renal disease (ESRD) worldwide. Diabetic kidney disease develops due to damage to intraglomerular arterioles and is one of the microvascular complications. Its prevalence is 30%–40% in type 1 diabetes and 25% in type 2 diabetes. The number of patients with diabetes accompanied by chronic kidney disease (CKD) increases with the increase in the prevalence of diabetes(1). The Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease (KDIGO) community recommends the use of the phrase "diabetes and chronic kidney disease" instead of diabetic kidney disease [glomerular filtration rate < 60 mL/(min · 1.73 m^2) and/or albuminuria] and diabetic nephropathy (pathological findings in kidney biopsy due to diabetes) to avoid errors in terminology. It would be more appropriate to use this expression, considering that other glomerulopathies are also reported in patients with diabetes.

Pathogenesis

The causes of renal damage are numerous and complex. The major ones are as follows:

1. Hemodynamic changes: These changes begin when hyperglycemia causes an increase in the levels of insulin-like growth factors, leading to dilatation in the afferent arterioles and an increase in the glomerular filtration rate. These growth factors cause mesangial enlargement and proliferation. The activation of renin-angiotensin and the vasoconstriction of the efferent arterioles trigger tubular damage by contributing to the increase in intraglomerular pressure and causing medullary hypoxia. Another effect of hyperglycemia is podocyte damage.
2. Changes in metabolic pathways: These metabolic pathways include polyol pathway, hexosamine pathway, protein kinase C pathway, advanced glycosyl-

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ation end-product pathway, and adenosine monophosphate kinase pathway.

3. Genetic and environmental factors: The risk has been found to increase in the first-degree relatives of patients with diabetes and diabetic kidney disease (2). Familial inheritance is associated with many genes. The most important of these is the angiotensin-converting enzyme (ACE) gene polymorphism (3). The environmental factors include smoking, low birth weight, sleep apnea syndrome, and foods containing fructose syrup.

Diagnosis

Diabetic kidney disease is diagnosed based on clinical and laboratory findings. It is asymptomatic, and hence the decrease in glomerular filtration rate (GFR) and/or microalbuminuria in routine examinations should be a warning. Microalbuminuria can be assessed in 24-h urine, or it can be requested as the albumin/creatinine ratio in the first urine in the morning. The diagnosis is made if the eGFR measured using one of the Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), or Cockroft–Gault formulas is below 60 mL/min and/or if the albumin/creatinine ratio is higher than 30 mg/g in two of the three urine samples requested within 3 months of persistence.

Microalbuminuria and low GFR can be seen temporarily in some cases. The tests should be planned later in the case of exercise, urinary infection, fever, uncontrolled hypertension, hypovolemia, hyperglycemia, and decompensated heart failure.

Chronic renal failure in patients with diabetes is staged according to the values of eGFR and albuminuria as in patients without diabetes.

Table 1. Classification of chronic renal failure in diabetic nephropathy

According to glomerular filtration rate	According to albuminuria amount
G1: Normal or high (≥90 mL/min)	A1: Normal–high normal (30 mg/g)
G2: Slightly decreased (60–89 mL/min)	A2: High (30–300 mg/g)
G3a: Mild to moderately decreased (45–89 mL/min)	A3: Very high (300 mg/g)
G3b: Moderate to severely decreased (30–44 mL/min)	
G4: Severely decreased (15–29 mL/min)	
G5: Renal failure (<15 mL/min)	

The algorithm followed for the diagnosis of Diabetic Kidney Disease (DKD) is summarized in Figure 1 (4).

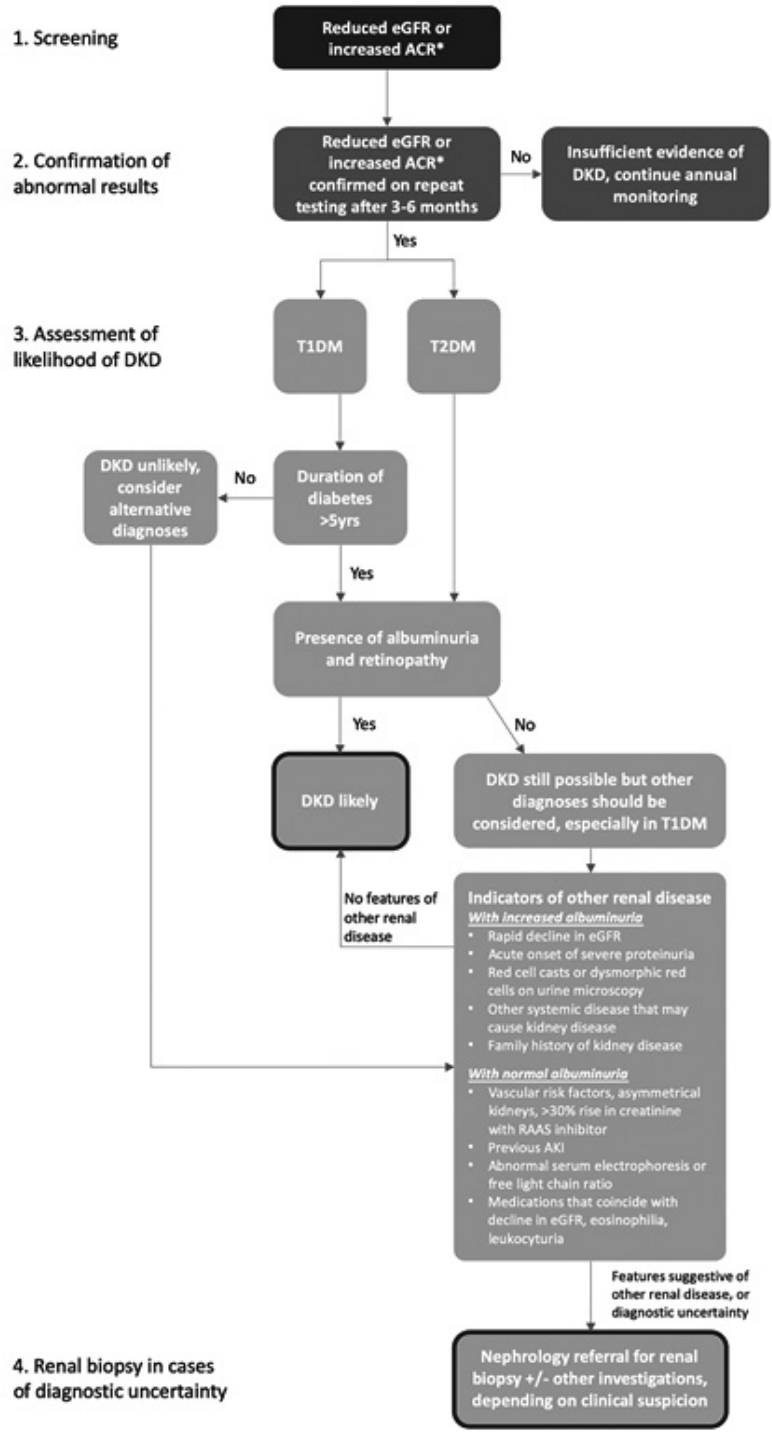

Figure 1. Diagnostic algorithm in diabetic nephropathy.

The recommendation of The Kidney Disease Improving Global Outcomes (KDIGO) and the American Diabetes Association is to screen for diabetic nephropathy with eGFR and urine albumin/creatinine ratio once a year, starting 5 years after the onset of diabetes in adults with type 1 diabetes, and once a year in type 2 diabetes, starting from diagnosis, since the time to diagnosis in type 2 diabetes can be long. The urinary albumin/creatinine ratio should be repeated every 3 or 6 months to monitor the progression of diabetic nephropathy in patients who develop microalbuminuria (4,5).

Renal biopsy is not routinely performed in the diagnosis. However, expanding the indications for kidney biopsy may be beneficial in obtaining more information and timely initiation of correct diagnosis and appropriate treatment. The indications for biopsy in a patient with diabetes are as follows:

1. If proteinuria develops in a patient with type 1 diabetes in less than 5 years.
2. If proteinuria without retinopathy occurs in type 1 diabetes (absence of retinopathy does not exclude DBH in type 2 diabetes).
3. If hematuria and/or active urinary sediment are reported.
4. If diabetic kidney disease steps are not observed (nephrotic proteinuria without the development of microalbuminuria).
5. If kidney functions that deteriorate rapidly without proteinuria are detected.
6. If signs of systemic disease (fever, arthritis, skin rashes, and so on) are reported.

The most common glomerular diseases in patients with diabetes are membranous glomerulonephritis, focal segmental glomerulonephritis, IgA nephropathy, minimal change disease, and acute poststreptococcal glomerulonephritis.

Table 2. Clinical stages of Diabetic Nephropathy and pathological changes in these stages

	Clinic	Pathology
Stage 1	Hyperfiltration stage: Normal GFR (125 mL/min) Normoalbuminuria (<30 mg/g)	Increased volume of glomerular capillaries and increased kidney weight due to interstitial hypertrophy
Stage 2	Silent stage: Normal GFR Normoalbuminuria Changes in biopsy	Thickening of the glomerular basement membrane Mild mesangial matrix increase

Stage 3	Microalbuminuria stage: Normal GFR Microalbuminuria (30–300 mg/g) Normal creatinine Hypertension can be observed	Severe diffuse and nodular (Kimmelstiel–Wilson nodules) enlargement in the mesangial matrix
Stage 4	Overt proteinuria: Proteinuria (more than 300 mg/g) Normal or increased creatinine level Hypertension	Increase in capillary wall thickness, mesangial enlargement, capillary constriction, and hyaline material deposition
Stage 5	Chronic kidney failure	Tubulointerstitial fibrosis

In recent years, it has been observed that progressive kidney disease develops without albuminuria, especially in male patients with type 1 diabetes. This condition, which is observed after the absence of any other kidney disease has been proven, is called nonalbuminuric diabetic kidney disease. Glomerular vasoconstriction that develops due to Tumor Necrosis Factor (TNF)-α receptor activation is held responsible. Macrovasculopathy, especially coronary artery disease, is more common. This strongly suggests that macrovasculopathy plays a role in the etiology (6).

Studies have found that hyperfiltration is associated with increased proteinuria and deterioration of kidney functions (7). This phase is reversible with blood sugar regulation (8). Renin-angiotensin system (RAS) blockers and sodium-glucose co-transporter (SGLT2) inhibitors have some benefits in hyperfiltration (9,10). However, due to their side effects, their routine use is not recommended when considering the profit–loss rate.

Prognosis

The mortality is 2.7 times higher in patients with diabetes with normoalbuminuria and 20–200 times higher in patients with overt proteinuria. Albuminuria has been found to be associated with endothelial damage, hypertension, hyperlipidemia, and high Cross Reactive Protein (CRP) levels, leading to a shortening of life expectancy by creating a tendency to atherosclerosis (11).

TREATMENT AND PREVENTION

Blood sugar regulation

Blood sugar regulation is the first and most important step in treatment. Despite shortcomings in the evaluation, HbA1c is still used because of its easy access and low cost.

The recommended HbA1c levels according to the stages are as follows.

Stage 1-3A (GFR 45 mL/min): <7

Stage 3B (GFR 30–44 mL/min): 7–7.5

Stage 4 (GFR 15–29 mL/min): 7–7.5

Stage 5D (GFR <15 mL/min and hemodialysis): 7.5–8

The target should be 7.5–8 in patients who have frequent episodes of hypoglycemia, have diseases that shorten their life span, and have serious micro – and macrovascular complications (12).

Insulin: All forms of insulin can be used in patients with diabetic nephropathy, but exogenous insulin is excreted by the kidney, and hence the dose should be reduced by 50% in those on dialysis.

Metformin and SGLT-2 Inhibitors**:** Oral antidiabetics should be preferred based on the characteristics of the patient. According to the KDIGO 2020 DM and CKD guidelines, metformin and SGLT-2 inhibitors are recommended as the first-line treatment after lifestyle changes. As indicated in Table 3, they should be discontinued in patients undergoing dialysis. The metformin dose should be reduced if GFR is less than 45 mL/min; it should not be used if it is less than 30 mL/min and in dialysis patients. Scientific data show that SGLT-2 inhibitors can be started when GFR is more than 30 mL/min. Empagliflozin and canagliflozin were shown to significantly reduce the development or worsening of nephropathy in the EMPA-REG OUTCOME study and the CANVAS, CREDENCE, and DECLARE-TIMI studies, respectively (13,14).

Glucagon-like peptide-1 agonists (GLP-1 agonists): GLP-1 agonists can be used as the second choice due to their protective effects on the cardiovascular system and kidney. They should not be used in Stage 5 CKD. LEADER and SUSTAIN studies using GLP-1 agonists reported that liraglutide and semaglutide, respectively, slowed the progression to nephropathy (15).

Dipeptidyl peptidase-4 (DPP-4) inhibitors**:** Although these inhibitors reduce albuminuria, their renal protective effects are unclear. Except for linagliptin, the dose should be reduced in Stage 5 CKD, discontinued in those on dialysis, and should not be given together with GLP-1 agonists.

Sulfonylurea**:** It increases insulin secretion independent of glucose level. Hence, care should be taken in dialysis patients and those with advanced kidney failure.

Thiazolidines**:** Although they are effective in regulating blood sugar levels in CKD, their use in dialysis patients should be limited due to their side effects such as edema and osteoporosis.

Alpha-glucosidase inhibitors**:** Acarbose and its metabolites undergo renal excretion and hence are not recommended in dialysis patients.

Table 3. Treatment preferences according to CKD stages

Option	Stage 1-3A CKD	Stage 3B CKD	Stage 4-5 CKD and dialysis patients
1	SGLT-2 Inhibitor +/– metformin	SGLT-2 Inhibitor +/– low-dose metformin	No special recommendations. Insulin, DPP-4 inhibitor, GLP-1 receptor agonist, sulfonylurea, glinides, and glitazone can be used with a focus on their side effects. Metformin, SGLP-2 inhibitors, and acarbose are contraindicated
2	GLP-1 Agonists	GLP-1 Receptor agonist	
3	DPP-4 inhibitors, sulfonylurea, glinides-glitazone, alpha-glucosidase inhibitors, and insulin	DPP-4 inhibitors, sulfonylurea, glinides-glitazone, alpha-glucosidase inhibitors, and insulin	

Blood pressure regulation

Hypertension is closely related to increased cardiovascular risk and albuminuria, and its treatment is essential. According to the 2019 Turkish Consensus on Hypertension Report, the target systolic blood pressure is 130–140 mm Hg for patients over 65 years of age and 120–130 mm Hg for patients 65 years of age and younger, while the diastolic blood pressure is 70–80 mm Hg for all patients.

The first choice in treatment should be RAS inhibitors. A 30% creatinine increase after the first dose should be considered as normal. The drug should not be stopped unnecessarily, and the maximum dose should be increased if possible. In the case of increases above this level, renal artery stenosis should be considered. Angiotensin receptor blockers and ACE blockers are both effective in DBH. The combined use of renin–angiotensin aldesterone inhibitors is not recommended. No additional cardiovascular benefit has been demonstrated. The antiproteinuric effect of RAS blockers can be enhanced by combining them with a low-sodium diet and diuretics.

The nondihydropyridine group antihypertensives provide a 30% reduction in basal proteinuria, but have no antiproteinuric effect in the dihydropyrine group (16).

Carvedilol and nebivolol, which do not have metabolic side effects from beta-blockers, can be given in addition to RAS blockers in patients with cardiac problems.

Spironolactone is antiproteinuric when used alone or in combination with RAS blockers, and its use is beneficial in these patients.

DYSLIPIDEMIA

High triglyceride levels and low high density lipoprotein (HDL) levels are associated with cardiovascular risk in patients with diabetes. It is also a risk factor for albuminuria. All lipid values should be brought into the target range. However, it should not be overlooked in the ACCORD study that the concomitant use of statins and fibrates did not reduce cardiovascular risk (17).

New drugs under study

The FIDELIO-DKD study showed that the progression to CKD was less with non-steroidal finerenone, one of the mineralocorticoid receptor antagonists. The hyperkalemic side effects of this preparation are also less (18).

The endothelin receptor antagonist atrasentan has been found to significantly reduce the progression to ESRD, and its future use is promising (19).

COCLUSION

Result of diabetic nephropathy is an epidemic disease with increasing frequency. As developments in the treatment of diabetes mellitus continue, prevention and treatment of nephropathy is expected to improve as well.

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