INTERNATIONAL JOURNAL OF
INTEGRATIVE AND
MODERN MEDICINE

The Main Approaches in the Treatment of Chronic Kidney Disease Based on International Recommendations

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Annotation: Diabetic nephropathy (DN) is a serious health problem. It occurs in 50% of people living with diabetes, is the main cause of terminal stage kidney disease (TSKD) requiring treatment with dialysis or kidney transplantation, and is associated with a significant increase in cardiovascular morbidity and mortality. DN is a clinical syndrome characterized by persistent albuminuria and progressive decrease in kidney function, but it is increasingly recognized that the manifestations and clinical course of kidney disease in diabetes are heterogeneous. The term "diabetic kidney disease" (DBP) is currently widely used to refer to people with diabetes who have either albuminuria or decreased kidney function. This article will discuss the clinical picture and approach to the diagnosis of DBP, as well as its prognosis. The general principles of DKD management will also be reviewed with reference to the current international recommendations.

Keywords: Nephropathy, glomerular filtration rate, diabetes mellitus, hyperglycemia.

Diabetes mellitus (DM) is a chronic non–communicable disease with an international epidemic scale. According to the World Health Organization (WHO), 422 million or 8.5% of the world's population over the age of 18 suffer from diabetes. According to the International Diabetes Federation (IDF), 537 million people with diabetes were registered in 2022. According to experts, by 2030 this figure may increase to 643 million, and by 2045 to 783 million [11]. It is known that the development of this disease consists of several stages, which is associated with the control of glycemia and blood pressure. However, despite the control of blood sugar levels, the prevalence of chronic kidney disease (CKD) in diabetic patients has not decreased over the past two decades. One of the most common vascular complications of diabetes is the development of diabetic nephropathy, which can end in end-stage renal failure (ESRD). For this reason, this disease remains a serious problem affecting a decrease in the quality of life and early death of patients with diabetes mellitus [8,9,10].

There are two main goals in the treatment of diabetic nephropathy :

- ✓ maintaining kidney function to reduce the risk of CKD;
- ✓ reducing the risks of cardiovascular events and mortality.

In addition, people with DBP are more likely to suffer from retinopathy, nephropathy, and diabetic foot syndrome, so it is important to be extra vigilant about these complications. Treatment recommendations have been developed by several international and national organizations and summarized in Table 2.

Table 2. Summary of treatment goals for key therapeutic goals in the international guidelines on diabetes and CKD

	KDIGO (2012)	EASD (2019)	ADA (2020)	NICE (2014)
Dietary sodium	<2 g/day (or <5 g/day of salt)	-	<2300 mg/day	-
Physical activity	>150 min/week, moderate intensity	>150 min/week of aerobic and strength training	Aerobic activity >150 min/week	>150 min/week, moderate intensity, aerobic activity
Weight Loss	Achieve a healthy weight (BMI 20-	Weight stabilization if	Weight loss >5% if BMI ≥ 25 kg /	Initial goal is 5-10 % weight loss if BMI ≥

	25 kg /m2)	BMI > 25 kg / m^2	m^2	25 kg/$m^{2.}$
Smoking cessation	recommended	Mandatory	We advise you to refrain from smoking tobacco and electronic cigarettes	recommended
Blood pressure	<130/80 in the presence of albuminuria	SBP < 130 mm Hg, but not <120 DBP < 80 mm Hg, but not <70 If >65 years: SBP 139-130 mmHg	<130/80 mmHg if the 10-year cardiovascular risk is ≥15% <140/90 if the risk is lower	<130/80 mmHg
RAASi	All patients with albuminuria	should take first-line antihypertensive medications, especially in the presence of albuminuria or LVH.	First-line antihypertensive drugs in the presence of albuminuria	First-line antihypertensive drugs in the presence of albuminuria
HbA1c **b**	<7% for most patients Higher target for the risk of hypoglycemia, severe comorbidities or limited life expectancy	<7% for most patients <6.5% for early-stage diabetes and younger patients <8% in the elderly or those with severe multimorbidity	<7% for most patients <6.5% at low risk of hypoglycemia <8% at high risk of hypoglycemia at multimorbidity	<7.0% at risk of hypoglycemia <6.5% at low risk of hypoglycemia Relax the target if: • High risk of hypoglycemia • Reduced life expectancy • Severe multi-morbidity • Elderly or weak
Lipid management	Statin therapy for all patients with diabetes and CKD	Statin therapy as first line Moderate cardiovascular risk: LDL cholesterol <2.6 mmol / l (100 mg / dl) High cardiovascular risk: LDL cholesterol < 1.8 mmol / L (70 mg / dl) Very high cardiovascular risk: LDL	High-intensity statin therapy for all patients aged 50-70 years with multiple risk factors for cardiovascular diseases. Moderate-intensity statins for patients aged 40-75 years without additional risk factors for cardiovascular disease.	Statin therapy for all patients with diabetes and CKD

		cholesterol < 1.4 mmol / L (55 mg / dl)		
Criteria for referral to a nephrologist	• CKD 4 stages • Progression of CKD	-	• CKD 4 stages • The renal diagnosis is unclear. • Rapid progression of CKD	• CKD 4 stages • Reduction of GFR >25% plus transition to the next category of CKD • Decrease in GFR >15 ml/min/1.73m2 over 12 months

Note. ADA, American Diabetes Association; BMI, Body mass Index; CKD, chronic kidney disease; CVD, cardiovascular system; DBP, diastolic blood pressure; EASD, European Association for the Study of Diabetes; GFR, glomerular filtration rate; HBA1C, hemoglobin A1C; KDIGO, Kidney diseases that improve global outcomes; LDL-low-density lipoprotein cholesterol; NICE, National Institute of Health and Excellence; RAASi, renin-angiotensin-aldosterone system inhibitors; SBP, systolic blood pressure.

The information provided here is only brief. The recommendations emphasize the need for an individual approach that includes careful consideration of the risks and benefits of therapy goals and discussion with patients. More detailed information can be found in the guidance documents. It should also be noted that the 2019 KDIGO Clinical Practice Guide for the Management of Diabetes in CKD, which may differ from the summary presented, is currently being finalized.

- [a]Albuminuria is defined as urinary albumin excretion >30 mg / day or equivalent (urinary albumin-to-creatinine ratio > 3 mg / mmol or > 30 mg / g).
- [b]HBA1C values: 8% = 64 mmol/mol; 7.0% = 53 mmol/mol; 6.5% = 48 mmol/mol.
- [c]Progression of CKD is defined as a decrease in GFR >25% plus transition to the next category of CKD; rapid progression is defined as a decrease in GFR >5 ml / min/1.73 m^2/ year.

Lifestyle management

Non-pharmacological interventions are an important concept of any strategy to improve outcomes in patients with Diabetes Mellitus and should include weight loss, increased physical activity, reduced dietary sodium intake, and smoking cessation. Unfortunately, these goals are very difficult to achieve, it is important to encourage patients to actively participate in their own management and to be supported in achieving mutually agreed treatment goals.

The onset of kidney disease in people with diabetes heralds a significant increase in the risk of cardiovascular mortality, and therefore aggressive modification of risk factors is justified in all patients. This includes quitting smoking and lowering lipid levels; the importance of lowering blood pressure is discussed later. There is ongoing debate about whether lipid-lowering therapy has a direct benefit in slowing the progression of diabetic nephropathy (DN). It has been suggested that in CKD, hyperlipidemia may contribute to glomerulosclerosis, and although some studies have suggested that lowering lipid levels may help preserve eGFR or reduce albuminuria, this has not been conclusively proven.

Glycemic control

Improved glycemic control has a beneficial effect on the development and progression of DN. DCCT randomized 1,441 people with T1DM to intensive insulin therapy (target HbA1c <6.05%, achieved

7.3%) or standard therapy (achieved HbA1c 9.1%). 79 After an average follow-up period of 6.5 years, there was a significant reduction in the development of moderate (A2) and severe (A3) albuminuria in the intensive group, as well as an improvement in the indicators of other microvascular complications. With further follow-up of participants after the control and intervention groups were transferred to intensive control targets, the development of moderate (A2) and severe (A3) albuminuria remained lower in the intensive group for another 4 years. 80 Evaluation of long-term outcomes also showed that intensive insulin treatment slowed eGFR decline and reduced the proportion of people who developed persistent eGFR decline to <60 ml / min/1.73m^2(a 50% reduction in risk with intensive care). 81 In addition, studies on kidney biopsies in people who have undergone pancreatic transplantation have shown that histological changes in diabetic glomerulopathy can be reversed, although this may take more than 10 years of normoglycemia. 82

For T2DM, the data is slightly more ambiguous. In the United Kingdom Prospective Diabetes Study (UKPDS), 3,867 people were randomly assigned to either intensive control (using oral medications or insulin) or diet control alone. The difference in HbA1c levels between the study groups was smaller (7.0% vs. 7.9%), and although overall performance improved in the intensive care group, there was no difference in the development of moderate or severe albuminuria or a doubling of serum creatinine. 83More positive results were obtained in the ADVANCE study, in which 11,140 people with T2DM were randomized to intensive (HbA1c 6.5%) or standard (HbA1c 7.3%) glycemic control. 84 Intensive control showed a reduction in combined macrovascular and microvascular complications and, in particular, a decrease in the incidence or deterioration of DN (4.1% vs. 5.2%; hazard ratio 0.79; 95% CI 0.66-0.93). This was defined as the development of severe (A3) albuminuria, a doubling of serum creatinine levels to at least 200 mmol / L, the need for renal replacement therapy (RRT), or death due to kidney disease. The effect was mainly due to a reduction in the development of severe (A3) albuminuria with a tendency to reduce the need for RRT or mortality from renal causes, but without a difference in doubling serum creatinine levels. The Diabetes Veterans Affairs Study also reported a reduction in the incidence or worsening of albuminuria with intensive and standard glycemic control (9.1% vs. 13.8%, respectively), although there were no differences between the groups for any other endpoints, including kidney deterioration. functional disorders, ESRD, cardiovascular events, or mortality. Conversely, the ACCORD trial, which randomized 10,251 people for intensive or standard glycemic control, was terminated prematurely due to higher mortality in the intensive care group and lack of evidence of benefit in the other groups. 86

Thus, intensive glycemic control can reduce the risk of DN and slow its progression, if it has already occurred, although at the expense of more hypoglycemic events. This is true for both types of diabetes, although the evidence is clearer in T1DM, and the benefit of more intensive glycemic control appears to be reduced in the later stages of DBP. However, intensive glycemic control does not completely eliminate the risk of DN, and there is no evidence that improved glycemic control reduces the risk of TSKD progression. Therefore, the goal of glycemic control should be personalized after careful discussion of individual risks and benefits.

In T2DM, the choice of a glucose-lowering drug is also important. SGLT2i has been strongly shown to reduce the risk of TSKD, doubling serum creatinine levels, or death from renal or cardiovascular causes (30% reduction in relative risk; hazard ratio 0.70; 95% confidence interval 0.59 to 0.82) in people with T2DM, albuminuria. DN (eGFR 30-90 ml / min/1.73m^2 and severe (A3) albuminuria) and taking RAAS inhibitors, 87 and are now recommended in the ADA guidelines: "SGLT2i should be considered in patients with type 2 diabetes and CKD who require another drug added to metformin to achieve the A1C target, or cannot use or tolerate metformin "32 and TSKD recommendations. 33 It should be noted that the nephroprotective effects of SGLT2i are largely independent of their hypoglycemic effects. These agents will not be discussed in more detail here, as they are covered in separate editorials elsewhere in this issue of the journal "*Diabetes, Obesity, and Metabolism"*.

Glucagon-like peptide 1 (GLP-1) receptor agonists may also have advantages and have the same recommendations for their use as ADA. 32 Data on the effect of GLP-1 agonists on DN are mainly derived from secondary results of studies on cardiovascular endpoints of relatively short duration. In

addition, these studies generally resulted in very small differences in glycemic control between the experimental and control groups, so it is unclear whether the effects are due to differences in glycemia or whether other mechanisms of action are more important. Liraglutide has been shown to cause fewer people to reach the combined renal endpoint of first-time severe (A3) albuminuria, doubling of serum creatinine, TSKD, or death due to kidney disease (RR 0.78, 95% CI 0.67–0.92), but this was almost entirely due to lower blood pressure. the frequency of severe (A3) albuminuria[25-26]. Dulaglutide has also been shown to lead to fewer people with T2DM and an increased cardiovascular risk, achieving a similar combined renal endpoint (18.4% vs. 20.6%, HR 0.87, 95% CI 0.79-0.95). 89 The study analysis also showed a decrease in the incidence of new severe (A3) albuminuria (8.9% vs. 11.3%, HR 0.77, 95% CI 0.68-0.87). In contrast, dipeptidyl peptidase-4 inhibitors do not appear to have any specific renoprotective effect, despite their mechanism of action that increases GLP-1 levels.

Maintaining the kidney function

Inhibition of RAAS is a cornerstone in the treatment of DN. In T1DM, landmark studies have clearly demonstrated the beneficial effects of angiotensin-converting enzyme (ACE) inhibitors. For example, in 235 people with normal blood pressure, T1DM, and moderate albuminuria who were randomly assigned to the captopril or placebo groups, captopril resulted in a reduced risk of severe (A3) albuminuria >60% and a smaller increase in the rate of albumin excretion. 91 Similar studies have confirmed these findings [33]. When captopril was evaluated in randomized controlled trials in T1DM patients with severe albuminuria and reduced eGFR, the risk of doubling serum creatinine levels was shown to be reduced by approximately 50%, with a greater degree of risk reduction observed in individuals with lower eGFR values. [34] Even in patients with nephrotic proteinuria, the use of ACE inhibitors leads to a decrease in urinary protein excretion to <1 g/24 h in most people.

In T2DM, the most convincing evidence for RAAS inhibition was obtained in studies of angiotensin receptor blockers (ARBs), in particular in the IDNT and RENAAL studies. IDNT randomized 1,715 people with T2DM, reduced GFR, and severe (A3) albuminuria to irbesartan, amlodipine, or placebo. 65 Irbesartan resulted in a reduced risk of approximately 20% at the combined endpoint of doubling serum creatinine, TSKD, or death from any cause compared to either of the other two study groups, effects that were independent of blood pressure. The RENAAL study showed similar results, in which losartan was compared with placebo in 1,513 people with DM2 and DN. 66 The composite endpoint of serum creatinine doubling, TSKD, or death was reduced by 16% in the losartan group, which also had a significantly lower rate of doubling of serum creatinine and ESRD when these endpoints were evaluated individually. The risk of hospitalization for heart failure also decreased. Similar results were replicated in Asian populations, 95 although there is some degree of uncertainty as to whether RAAS inhibition in T2DM slows the progression from moderate (A2) albuminuria to overt DN regardless of the effects of lowering blood pressure. However, it is likely that ACE inhibitors have a similar effect on ARBs in T2DM, as shown in the secondary analysis of the ADVANCE 96 study and RCT, in which 250 people with T2DM and moderate (A2) albuminuria were randomized to receive telmisartan or enalapril. 97 After 5 years, similar rates of deterioration of the measured GFR were observed and there were no differences in other indicators of the outcome of DN. In some of these studies, it is also clear that a greater degree of albuminuria reduction in response to RAAS inhibitors is associated with better outcomes, and these results are observed in different blood pressure categories, demonstrating that albuminuria reduction is protective. 98 This has led to the suggestion that ACE inhibitors and ARBs, or one of these agents in combination with direct renin inhibitors, may provide additional benefits by significantly reducing albuminuria. In fact, when tested in RCTs (ONTARGET and VA-NEPHRON-D), double blockade of RAAS did not lead to improved outcomes, but resulted in a higher incidence of side effects, including hyperkalemia and AKI.[28-32] Therefore, a double blockade of the RAAS should be avoided. Conversely, there are patients for whom the use of RAAS inhibitors is impractical or their dose is limited due to hyperkalemia; agents such as sodium zirconium cyclosilicate and patiromer are now available for the treatment of hyperkalemia, although it remains to be seen whether these agents improve hard endpoints, allowing for increased RAAS inhibition.[13-18] Therefore, RAAS inhibition should be offered to people with T1DM or T2DM with

hypertension, high / normal blood pressure and moderate (A2) or severe (A3) albuminuria, as well as people with reduced eGFR.

Controlling hypertension is fundamental to reducing the risk of CKD progression and reducing cardiovascular risk. This was confirmed in a meta-analysis involving 40 RCTs with more than 100,000 participants, which reported that for every 10 mmHg decrease in systolic blood pressure, there was a 17% reduction in the risk of mortality, an 11% reduction in cardiovascular events, and the development of albuminuria[16-21] These effects were largely the same for different classes of antihypertensive drugs. In addition to RAAS inhibitors, the only antihypertensive agents that can have an additive effect on reducing albuminuria are non-dihydropyridine calcium channel blockers, diltiazem and verapamil. Bakris et al. randomized 52 people with DM2, DN, and hypertension to receive an ACE inhibitor, a non-dihydropyridine calcium channel blocker, or a beta blocker. 103 These effects were similar in the ACE inhibitor and calcium channel groups, with a greater reduction in albuminuria compared to the beta-blocker group. However, reducing albuminuria with diltiazem or verapamil has not been shown to improve results. There is broad consensus among the recommendations that people with diabetes and albuminuria should have their blood pressure reduced to <130/80 mmHg to achieve optimal kidney and cardiovascular protection (Table 2), although less stringent goals should be considered for individuals prone to postural hypotension. . Dietary salt restriction may also be an effective component of blood pressure management, and the ADA guidelines suggest a daily sodium intake of <2,300 mg. 32

Combined interventions

In clinical practice, people with diabetes should be evaluated and treated comprehensively, with reduced risk and intervention for the entire spectrum of macro-and microvascular complications. The Steno-2 study showed that combined intervention in T2DM resulted in a number of benefits, including improved survival, reduced cardiovascular events, and slower progression of DN. During the study, 160 people with T2DM and moderate (A2) albuminuria were randomized to standard treatment or phased introduction of behavioral modification and pharmacological treatment for hyperglycemia, hypertension, dyslipidemia and microalbuminuria. Due to the nature of the intervention, blinding was impossible. Significantly lower rates of progression of nephropathy, retinopathy, and autonomic neuropathy were observed (odds ratio of severe (A3) albuminuria 0.27, 95% diabetes insipidus DI 0.1-0.75), as well as greater reductions in albumin excretion and cardiovascular events. Further analysis of the results after the randomized phase of the study showed a significant reduction in all-cause mortality (HR, 0.54; 95% CI, 0.32–0.89), as well as a slower rate of GFR decline (3.1 ml / min / year in the intensive care group compared to 4.0 ml / min / year in the traditional therapy group) and indicates a reduced risk of progression to ESRD (adjusted risk ratio in the intensive group 0.36, 95% DI 0.12-1.05) [31,32]. There are few data on the study of such approaches in T1DM. A final consideration is the introduction of interventions that have been proven effective in trials into "real" clinical practice. A number of observational studies have reported how difficult this can be, how there are differences between individuals in how easily treatment goals can be achieved, and that failure to meet treatment goals is associated with higher rates of DBP progression [33-34]

Conclusion. Diabetic kidney disease is a serious public health problem that complicates the course of many people living with diabetes and is the main cause of ESRD. The presence of DBP is also strongly associated with cardiovascular events and has a large impact on survival. Its manifestations and prognosis are not uniform and vary from person to person, such as non-albuminuric DBP and high rates of albuminuria regression, while the severity of albuminuria, especially in combination with high blood pressure, remains an important marker for individuals at higher risk. progressions. Treatment of DAP requires a holistic approach that combines reduced cardiovascular risk with elements of slowing the progression of kidney disease, such as glycemic control, RAAS inhibition, and lowering blood pressure. Effective implementation of these interventions in combination reduces the risk of progression of DBP, as well as other microvascular complications, cardiovascular events, and mortality. Several international groups have issued clinical guidelines that largely coincide with the recommended goals, and in clinical practice they should be adapted for each individual patient.

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