

Prevalence and Management of Diabetic Nephropathy in Western Countries

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Key Words

Diabetic nephropathy · Chronic kidney disease · Glomerular hyperfiltration · Microalbuminuria · Macroalbuminuria

Abstract

Background: Diabetic nephropathy (DN) often results in end-stage renal disease, and this is the most common reason for initiation of dialysis in the United States. Complications of diabetes, particularly renal disease, substantially increase the risk of subsequent severe illness and death. The prevalence of DN is still rising dramatically, with concomitant increases in associated mortality and cardiovascular complications. **Summary:** Renal involvement in type 1 and type 2 diabetes reflects a complex pathogenesis. Various genetic and environmental factors determine the susceptibility and progression to advanced stages of the disease. DN should be considered in patients who have had type 1 diabetes for at least 10 years with microalbuminuria and diabetic retinopathy, as well as in patients with type 1 or type 2 diabetes with macroalbuminuria in whom other causes for proteinuria are absent. The glomerular characteristic features include mesangial expansion, thickened glomerular basement membrane, and hyalinosis of arterioles. The optimal therapy of DN continues to evolve. For all diabetic patients, practical management including blood glucose and blood pressure control with renin-angiotensin-aldosterone blockade combined with lipid control, dietary salt restriction, lowering the

dietary protein intake, increased physical activity, weight reduction, and smoking cessation can reduce the rate of progression of nephropathy and cardiovascular disease. **Key Messages:** DN is a complex disease linking hemodynamic and metabolic pathways with oxidative stress, and systemic inflammation. We summarize the current evidence of epidemiology, clinical diagnosis, and the current management of DN in Western countries. **Facts from East and West:** The prevalence of DN is increasing in Asia and Western countries alike. The deletion (D) allele of the angiotensin-converting enzyme gene is associated with progression to end-stage renal disease in Asian patients with DN, but this association is uncertain in Europeans. An association between DN and polymorphism of the gene coding for acetyl coenzyme A carboxylase β has been reported in Asian and Western populations. Both in Japan and the US, criteria for diagnosis are a 5-year history of diabetes and persistent albuminuria. Renal biopsy should be done in patients with severe hematuria, cellular casts and – in the US – hepatitis and HIV to rule out other pathologies. Diabetic retinopathy is considered a key criterion in Japan, but the absence of it does not rule out DN in the US. Enlargement of the kidney is observed as a diagnostic criterion in Japan. The differential use of renal biopsy

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as diagnostic tool might account for a different prevalence between Asian countries. Some Japanese diabetic patients show typical histological alterations for DN with a normal ACR and GFR. The clinical classification is similar between Japan and the US including five stages based on ACR and GFR. The Japanese guidelines do not include blood pressure values for the classification of DN. Guidelines for DN treatment are evolving quickly both in Asia and Western countries based on the numerous clinical trials performed worldwide. Targeting the angiotensin system for its hemodynamic and nonhemodynamic effects is a common approach. DPP-4 inhibitors are widely used in Japan and might have a higher glucose-lowering effect in Asian patients due to their specific diet. A randomized, double-blind placebo-controlled study has been launched to assess the efficacy of the Chinese herbal tea extract Shenyan Kangfu in DN.

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Prevalence and Risk factors

Globally, an estimated 387 million people, or 8.3% of the population, have diabetes according to the International Diabetes Federation (IDF) Diabetes Atlas update of 2014. It is estimated that by the year 2035, 592 million people, or 1 person in 10, will have diabetes. The number of people with type 2 diabetes is increasing in every country, including the United States, where approximately 29.1 million people, or 9.3% of the population, are estimated to have diabetes. The prevalence of diagnosed diabetes is higher in racial and ethnic minorities among people aged >20 years, affecting approximately 15.9% of Native Americans, 13.2% of African-Americans, and 12.8% of Hispanics [1]. Diabetes accounted for approximately 45% of patients with end-stage renal disease (ESRD) in the US Renal Data System in 2013 [2]. Rates of all diabetic complications declined between 1990 and 2010 in the United States, with relative declines in acute myocardial infarction by 67.8%, death from hyperglycemic crisis by 64.4%, stroke by 52.7%, amputations by 51.4% and ESRD by 28.3% [3]. Reductions in these complications in adults with diabetes do not significantly reduce the overall burden of diabetes-related complications because of the large increase in the number of prevalent cases. Thus, the prevalence of diabetic nephropathy (DN) is still rising dramatically, with concomitant increases in associated mortality and cardiovascular complications [4].

The onset of DN in type 1 diabetes is typically between 10 and 15 years after the initial diagnosis, with the duration of prepubertal diabetes tending not to contribute as

significantly to the risk. The incidence of DN from type 1 diabetes has declined over the past three decades. Patients with type 2 diabetes have a more variable natural history and often a delayed diagnosis of diabetes. Many factors including hypertension, insulin resistance, and hyperlipidemia affect the albumin excretion rate (AER). However, the overall clinical course is similar in DN patients with type 1 and type 2 diabetes.

Both environmental and genetic factors have been postulated as DN risk factors. Risk factors affecting the progression of DN include baseline AER, age, hemoglobin A1c (HbA1c), blood pressure (BP), serum cholesterol, smoking, use of renin-angiotensin system (RAAS) blocker and genetic predisposition. Genetic factors conferring a predisposition to DN have been sought, but reproducible high-impact loci have not yet been identified. Several genetic strategies have been used to identify common disease risk loci and genes, including candidate gene analyses, family-based linkage analysis, transmission disequilibrium testing, population-based admixture mapping, and genome-wide association studies [5].

Pathophysiology

Many pathophysiological mechanisms have been postulated as initiation and progression factors. Two main pathways have served as cornerstones for study [6].

Hemodynamic Pathways

Hemodynamic pathways contributing to DN involve the activation of the local RAAS in proximal tubular epithelial cells, mesangial cells, and podocytes. Angiotensin II (ATII) predominantly acts as a vasoconstrictor at the level of the glomerular efferent arteriole, leading to increased glomerular capillary pressures. ATII also stimulates renal growth and fibrosis through ATII type 1 receptors, which contributes to mesangial matrix expansion, podocyte injury, and nephron loss [7]. Moreover, the activation of various vasoactive cytokines and growth factors, including transforming growth factor β (TGF- β), nitric oxide, vascular endothelial growth factor (VEGF), and endothelin play important roles in both the observed hemodynamic changes and aberrant molecular signaling in DN.

Metabolic Pathways

Hyperglycemia can directly result in mesangial expansion and injury by increasing intracellular glucose avail-

Table 1. Clinical stages of DN

	Designation	Characteristics	GFR	AER	BP
Stage 1	Hyperfunction	Glomerular hyperfiltration	Increased	May be increased	Normal
Stage 2	Silent stage	Thickened basement membrane Mesangium expansion	Normal	<30 mg/24 h or g/mg creatinine	Normal
Stage 3	Incipient	Microalbuminuria	GFR begins to fall	30–300 mg/24 h or g/mg creatinine	High
Stage 4	Overt DN	Macroalbuminuria	<60 ml/min/1.73 m ²	>300 mg/24 h or g/mg creatinine	High
Stage 5	Advanced nephropathy	ESRD	0–15 ml/min/1.73 m ²	Decreasing	High

ability, leading to the activation of signaling cascades favoring glomerulosclerosis, including pathways mediated by TGF- β , advanced glycosylation end products (AGEs), protein kinase C, and various cytokines and growth factors [8]. Decreased phosphorylated p38 (pp38) mitogen-activated protein kinase (MAPK) after chronic glucose loading can also contribute to podocyte cytoskeletal alterations and the development of abnormal albuminuria [9].

High glucose can bind reversibly and eventually irreversibly to free amino groups on circulating and kidney tissue proteins to form AGEs. AGEs form complex cross-links which accumulate over years of hyperglycemia. They activate specific receptors, inducing cellular dysfunction and tissue injury. AGE receptor activation stimulates the synthesis of growth factors and cytokines, which contribute to the accumulation of glomerular extracellular matrix proteins, albuminuria, and renal injury [10]. Moreover, metabolic pathways activating the renal immune system and inflammation response produce inflammatory cytokines [TGF- β , interleukin 1 (IL-1), IL-6, IL-18] and growth factors [VEGF, tumor necrosis factor- α (TNF- α)], which have all been implicated in renal disease progression.

Clinical Diagnosis

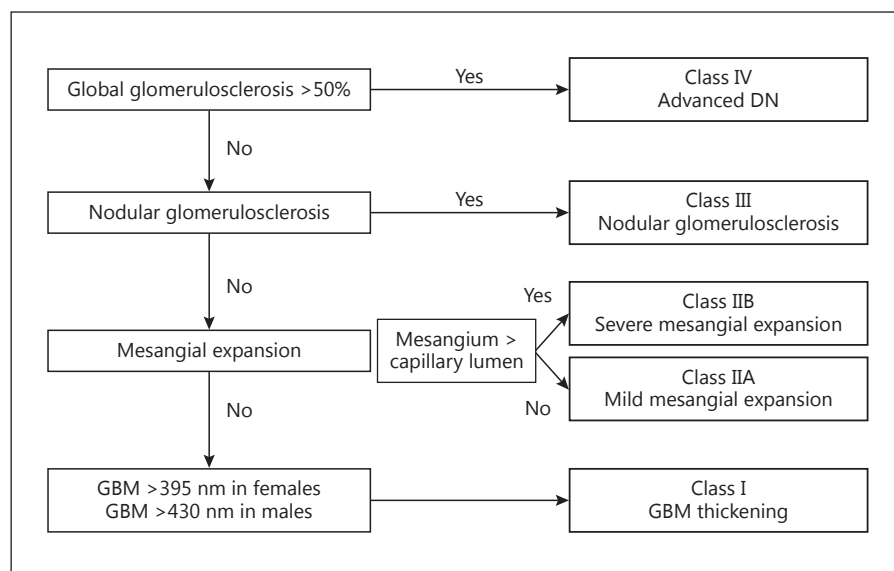
Clinically, DN has been characterized by a progressive increase in AER, a decline in GFR, and an increase in BP. More recently, and with the increasing use of RAAS blocker in diabetic patients, DN with normoalbuminuria or low microalbuminuria but declining eGFR has been described [11]. Renal involvement is diagnosed to be secondary to diabetes in the setting of long-standing diabetes with diabetic neuropathy or diabetic retinopathy particularly in type 1 diabetics, where there is a good correlation. Renal manifestations in diabetes are classified into five stages including glomerular hyperfiltration,

normoalbuminuria, microalbuminuria, macroalbuminuria, and finally ESRD (table 1). The earliest stage begins initially with glomerular hyperfiltration and increased GFR. The next stage is microalbuminuria, defined as a persistent AER rate between 30 and 300 mg/day. Microalbuminuria is a strong predictor for progressing to overt nephropathy and developing cardiovascular events [12], but some patients can spontaneously regress from microalbuminuria to normoalbuminuria [13]. Macroalbuminuria, defined as AER >300 mg/day, is considered a disease state with a high risk of progression to impaired GFR or irreversible kidney disease. It also is associated with a high cumulative incidence of ESRD (75%) at 15 years of follow-up [14]. A recent study reporting on long-term renal outcomes in patients with type 1 diabetes who developed incident macroalbuminuria during the DCCT trial found that the cumulative incidences of chronic kidney disease (CKD) and ESRD were only 32 and 16%, respectively, 10 years after diagnosis [15]. This supports the observation that reductions in AER are common, with more than half of type 1 diabetic patients with macroalbuminuria regressing to persistent AER <300 mg/day after long-term follow-up. This finding suggests that the clinical course of nephropathy in diabetic patients is modifiable, includes frequent AER reduction, and at times, complete regression of albuminuria. Thus, in many patients, control of risk factors of disease progression, including glycemic and hypertensive control, may achieve stabilization of renal function for long periods of time.

Diagnostic Criteria

The clinical practice guidelines for DN outlined by the Kidney Disease Outcomes Quality Initiative (KDOQI) recommend that screening for DN should begin 5 years after the diagnosis of type 1 diabetes and at the time of the diagnosis of type 2 diabetes [16]. It is common to find

Fig. 1. Glomerular pathological classification in DN. GBM = Glomerular basement membrane.



renal involvement in a type 2 diabetic patient at or soon after the initial diagnosis of diabetes. This is presumably due to the presence of type 2 diabetes for considerable periods of time before it is actually discovered, particularly for individuals without consistent health screening. The preferred screening tests include serum creatinine for calculating eGFR and an AER with a first-morning void spot collection. If the AER is abnormal, the test should be repeated to assess for persistence. Microalbuminuria is present if two of three AER tests are between 30 and 300 mg/day over a 6-month period. Diabetes is the likely cause of albuminuria in patients with persistent microalbuminuria or macroalbuminuria who have had diabetes for at least 10 years and/or diabetic retinopathy. In patients with diabetes, the presentation of a rapidly rising urinary protein level, a more rapid loss of renal function (≥ 1 ml/min/month), active urine red cell or white cell casts, gross hematuria, systemic signs and/or symptoms of other glomerular diseases, known chronic infections such as HIV or hepatitis B or C, and/or renal impairment without diabetic retinopathy should lead to the consideration of renal biopsy. While the presence of diabetic retinopathy strongly correlates with overt nephropathy and declining GFR <30 – 60 ml/min/ 1.73 m² [17], the association is not as strong in early and type 2 diabetes as it is in type 1 diabetes. Therefore, the lack of diabetic retinopathy does not rule out DN, particularly in type 2 diabetes. Additional treatable renal diseases may also be observed on a background of diabetic nephropathy [18].

Renal Pathology

Early diabetic pathological changes before the onset of microalbuminuria are mesangial expansion and glomerular basement membrane thickening [19]. More advanced disease may include the nodular glomerulosclerosis lesion, first described by Kimmelstiel and Wilson in 1936, hyalinosis of afferent and efferent arterioles, glomerular capillary subendothelial hyaline (hyaline caps), capsular drops along the epithelial parietal surface of the Bowman capsule, or combinations of these. The pathological DN glomerular lesions have recently been classified into four classes. Class I consists of electron microscopically confirmed thickening of the glomerular basement membrane, adjusted for gender and age. Class II consists of mild (IIA) to severe (IIB) mesangial expansion. Class III consists of nodular glomerulosclerosis, and class IV consists of $>50\%$ global glomerulosclerosis along with lesions of classes I, II, or III (fig. 1) [20]. In addition, in this new pathological DN classification, tubulointerstitial and vascular lesions are scored separately on scales of 0–3 and 0–2, respectively. Tubulointerstitial changes are a strong predictor of the decline of GFR in DN [21]. Theoretically, identifying renal tubular biomarkers that would enable additional risk stratification of this setting for propensity to GFR loss and ESRD would seem to help focus more intensive therapeutic interventions on patients who are at the highest risk of progressive DN [22]. However, so far, that promise remains unrealized [23].

Treatment

The optimal therapy of DN continues to evolve. The keystones in preventing and slowing renal progression are tight glycemic control, BP and lipid control, and other adjunctive interventions. The following sections summarize the clinical evidence supporting current therapeutic interventions.

BP Control

BP lowering has clearly shown to be an important and powerful intervention in slowing DN progression, reducing cardiovascular disease events, and preventing premature death in both type 1 and type 2 diabetic patients. However, the optimal lower limit for BP control in DN remains unclear. Major guidelines published before the Action to Control Cardiovascular Risk in Diabetes BP (ACCORD BP) trial suggested that the target BP in diabetic patients should be <130/80 mm Hg. However, in the ACCORD BP trial, there was no difference in the risk of composite major cardiovascular events between targeting a systolic BP <120 mm Hg and systolic BP <140 mm Hg [24]. Importantly, higher rates of serious adverse events attributed to the low BP target, including impaired renal function and hyperkalemia, were found among type 2 diabetic patients with high cardiovascular risk [24]. A recent systematic review suggested that a BP target of <125/75–130/80 mm Hg may be beneficial in adult patients with CKD and proteinuria >300–1,000 mg/day [25]. The KDIGO 2012 Clinical Practice Guideline for the management of BP in CKD recommended thresholds to initiate treatment to lower the BP to 130/80 and 140/90 mm Hg for DN patients with and without AER >30 mg/day, respectively [26]. Overall, it is recommended to individualize BP targets and agents taking into account age, coexistent cardiovascular disease and other comorbidities, risk of progression of CKD, the presence or absence of retinopathy, and tolerance to treatment regimens. In addition, KDIGO also suggests tailoring BP treatment regimens in elderly patients with CKD by carefully considering age, comorbidities and other therapies, and closely monitoring for adverse events related to hypotension.

RAAS Blockers

RAAS blockade is highly effective and should be utilized as first-line antihypertensive agent, particularly in patients with albuminuria. RAAS blockade confers benefits extending beyond simple BP reduction in hypertensive diabetic patients.

RAAS Blockade in Type 1 Diabetes

In type 1 diabetes with persistent microalbuminuria, angiotensin-converting enzyme inhibitors (ACEi) reduce the risk of nephropathy [27]. The Collaborative Study Group [28] compared captopril with placebo in patients with type 1 diabetes, urinary protein excretion >500 mg/day and serum creatinine >1.5 mg/dl. Captopril significantly reduced the composite risk of doubling serum creatinine, death, dialysis, or transplantation. There are no equivalent large long-term clinical trials to demonstrate the efficacy of ARBs in patients with type 1 diabetes with nephropathy. Nevertheless, based on the similar properties of ACEi and ARBs, there is sufficient reason to believe that both are effective in the treatment of type 1 DN.

In patients with normotensive and normoalbuminuric type 1 diabetes, early RAAS blockers in patients with type 1 diabetes did not demonstrate a substantial benefit on renal progression [29]. Currently, no evidence supports using a RAAS blocker for preventing nephropathy in normoalbuminuric diabetic patients with normal BP.

RAAS Blockades in Type 2 Diabetes

In the HOPE trial, in hypertensive normoalbuminuric patients with type 2 diabetes, ACEi demonstrated a significant reduction in the risk of nephropathy, stroke, and cardiovascular morbidity and mortality [30]. The BENEDICT trial showed that the use of an ACEi was associated with a decreased risk of microalbuminuria among type 2 diabetic patients with hypertension [31]. After following the cohort of the ADVANCE trial for a total of 10 years, including the in-trial period and the post-trial follow-up, there were significant reductions in the rates of death from any cause and from cardiovascular causes resulting from the 4.5-year period of BP control with perindopril and indapamide, but there were no cumulative benefits with respect to any other secondary outcome, including major microvascular events and ESRD [32].

In the stage of microalbuminuria, the IRMA 2 study demonstrated that the ARB reduced the progression to overt nephropathy by 70% in hypertensive type 2 diabetic patients during a 2-year follow-up period [33]. RAAS blockade is recommended to slow the progression from microalbuminuria to overt proteinuria.

In the stage of macroalbuminuria, two landmark trials demonstrated a clear benefit for ARBs in the treatment of type 2 diabetes with overt nephropathy. In the IDNT tri-

al, in 1,715 type 2 diabetic patients with overt nephropathy, irbesartan was associated with a risk reduction of doubling plasma creatinine by 37% and ESRD by 23%, compared with amlodipine [34]. In the RENAAL trial, in 1,513 type 2 diabetic patients with overt nephropathy, losartan also reduced the primary composite end points including lowering the incidence of serum creatinine doubling by 25% and ESRD by 28% [35]. Both clinical trials support the benefit of ARBs beyond BP control for slowing progressive renal functional decline in type 2 diabetes.

ACEi versus ARB Treatment

Compared with ARBs, data on the efficacy of ACEi in type 2 DN are less strong, largely because the studies were underpowered or follow-up was short. Nevertheless, some studies reveal that ACEi use results in greater reduction in albuminuria and a slower decrement in GFR decline compared with other antihypertensive agents. In the DETAIL trial, enalapril was compared with telmisartan in 250 diabetic patients with early nephropathy at 5 years. Both treatments had a similar impact on the decline in albuminuria, GFR, and ESRD [36]. The results support the clinical equivalence of ARBs and ACEi treatment in diabetic patients with nephropathy.

RAAS Blocker Combinations

Theoretically, dual RAAS blockade should be more effective than a single agent in the treatment of DN [37], but the results of both the ONTARGET trial and the VA-NEPHRON-D trial failed to support combined therapy with an ACEi and an ARB for preventing disease progression, especially ESRD, cardiovascular diseases, and mortality [38, 39]. In addition, in the ONTARGET study, dual RAAS blockade was associated with more end points, including the need for acute dialysis, doubling of serum creatinine, severe hyperkalemia, and death, than monotherapy [38]. Dual RAAS blockade was also associated with an increased risk of serious adverse events including acute kidney injury and hyperkalemia in the VA-NEPHRON-D study [39].

Aliskiren is an oral direct renin inhibitor that reduces plasma renin activity. Aliskiren combined with an ARB in the AVOID trial reduced albuminuria in type 2 diabetes more than an ARB alone, independent of its BP-lowering effects [40]. However, in a follow-up study

(ALTITUDE trial), aliskiren plus standard-of-care RAAS blockade in high-cardiovascular-risk patients with type 2 diabetes did not reduce cardiovascular events, as compared with placebo. This clinical trial was terminated prematurely because of a larger number of adverse events in the combination therapy group, including nonfatal stroke, hypotension, hyperkalemia, and renal complications [41]. Current guidelines document that there is insufficient evidence to recommend combining ACEi with ARBs or direct renin inhibitors to prevent progression of CKD [42], and dual RAAS blockers are not recommended in patients with diabetes [43].

RAAS Blockade Monitoring

Patients treated with ACEi or ARBs should be monitored for hypotension, decreased GFR, and hyperkalemia within 1 week of initiating therapy and/or increasing the dose. In most patients, as long as the GFR decline over 4 months is <30% from baseline and the serum potassium remains <5.5 mEq/l, then the ACEi or ARBs can be continued. In some studies, a decline of eGFR <30% is associated with long-term renoprotection, and therefore the RAAS blockade should not necessarily be stopped in these patients. Increases in serum creatinine concentration >30% after RAAS blockade initiation should raise the suspicion of bilateral renal artery stenosis. ACEi and ARBs should be used with caution in the setting of low GFR levels, hyperkalemia, bilateral renal artery stenosis, and women not practicing contraception.

Glycemic Control

Glycemic control can prevent early glomerular hyperfiltration and microalbuminuria [44, 45], and it can slow progression in diabetic patients with overt nephropathy [46]. However, few studies address intensive glycemic control in patients with advanced DN in whom it may be difficult to show a benefit. The efficacy of glycemic control as a renoprotective strategy depends in part upon the stage of renal disease.

Type 1 Diabetes

Intensive glycemic control (mean HbA1c 7%) in the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) cohort has been shown to reduce

the development of microalbuminuria by 39% and the development of macroalbuminuria by 54% [44]. The lower incidence of CKD was detected after more than 10 years, beyond the period of the DCCT treatment intervention [47]. Thus, early and long-term glycemic control is the most important preventive measure and treatment of kidney disease in type 1 diabetes. Moreover, after 10 years, the complete correction of hyperglycemia with pancreatic transplantation in type 1 diabetes led to a significant reduction in basement membrane thickening and mesangial expansion demonstrated on repeat renal biopsies [48].

Type 2 Diabetes

In the United Kingdom Prospective Diabetes Study (UKPDS) trial, in 3,867 patients with newly diagnosed type 2 diabetes, intensive glucose therapy (mean HbA1c 7.0%) conferred a lower risk of microvascular complications than conventional dietary therapy (mean HbA1c 7.9%) [45]. During 10 years of post-UKPDS trial follow-up, a continued reduction in microvascular and macrovascular events, including myocardial infarction and death from any cause, were observed in patients with intensive glucose therapy [49]. Benefits, described as a 'legacy effect', persisted despite the early loss of within-trial differences in HbA1c levels between the intensive-therapy and the conventional therapy groups. These observations indicate that intensive glucose control starting at the time of diagnosis is associated with a significantly decreased risk of all major vascular complications and mortality.

Three landmark trials including the ACCORD, ADVANCE, and VADT trial which targeted lower HbA1c goals (<6–6.5%), did not show a benefit of tight glycemic control for macrovascular complications or mortality in elderly patients with long-standing type 2 diabetes [50–52]. In a post-ADVANCE trial follow-up evaluation, there was a significant cumulative benefit with respect to ESRD, but no differences were observed in the risk of death from any cause or cardiovascular events between the intensive-glucose control and the standard-glucose-control groups [32]. Moreover, in the ACCORD trial, tight glycemic control was associated with a 22% increase in mortality from any cause [50]. Therefore, current clinical trials have not supported the effects of intensive glucose lowering for the prevention of cardiovascular events or mortality in patients with type 2 diabetes mellitus. Finally, a large systematic review

Table 2. HbA1c level in patients with advanced CKD and ESRD

Falsely increased HbA1c	Falsely decreased HbA1c
Carbamylated hemoglobin	Shortened life span of red blood cells
Increased glycosylation rate Uremia Metabolic acidosis	Blood transfusions
	Hemoglobinopathy
	Erythropoiesis supplement

concluded that tight glycemic control delays the onset of microalbuminuria and macroalbuminuria but does not reduce the incidence of ESRD [53].

In advanced CKD, both uremic toxins and the dialysis procedure itself can complicate glycemic control, with alterations that may predispose to both hyperglycemia and hypoglycemia. Advanced CKD and ESRD patients may develop severe insulin resistance due to deficiency of active vitamin D, secondary hyperparathyroidism, and glucose loading during dialysis, particularly in peritoneal dialysis. In contrast, deficient renal gluconeogenesis, uremic malnutrition, deficient catecholamine release, extended half-lives of some glucose-lowering medications, and impaired renal insulin degradation and clearance can contribute to hypoglycemia in this population [54]. Together, all of these factors contribute to wide fluctuations in blood glucose levels. Therefore, glycemic control must be individualized in DN patients and precaution is advised due to the risk of hypoglycemic events.

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommended that the target HbA1c level for diabetic patients with CKD should be ~7% to delay the progression of microvascular complications of diabetes. It is also stated that target HbA1c levels >7.0% are acceptable in individuals with multiple comorbidities, a limited life expectancy, and/or an increased risk of hypoglycemia [42]. However, this recommendation is not strongly evidence-based, since few studies address the benefits and risks of intensive glycemic control in advanced CKD or ESRD [42]. In patients with CKD and diabetes, glycemic control should be part of a multifactorial intervention strategy addressing BP control and cardiovascular risk, promoting the use of RAAS blockers, statins, and antiplatelet therapy where clinically indicated.

Table 3. Hypoglycemic agents in diabetes patients with CKD

Class	Drugs	Dosing recommendations		Complications
		stage 3 and 4	stage 5 and dialysis	
Sulfonylureas	Glipizide	No dose adjustment	No dose adjustment	Hypoglycemia
	Glyburide	Avoid	Avoid	Hepatitis, pancytopenia, hyponatremia, nausea, rash
	Glimepiride	Initiate at low dose, 1 mg po QD	Avoid	Hemolytic anemia, thrombocytopenia, agranulocytosis, dizziness, headache, skin rash
Alpha-glucosidase inhibitors	Acarbose	Avoid in patients with serum creatinine >2 mg/dl	Avoid	Ileus, hepatic toxicity, thrombocytopenia, diarrhea
Biguanides	Metformin	Avoid when GFR <30 ml/min/1.73 m ² Probably safe when GFR ≥45 ml/min/1.73 m ²	Avoid	Lactic acidosis
Meglitinides	Repaglinide	Ccr 20–40 ml/min: 0.5 mg before meals, titrate with caution Ccr <20 ml/min: not defined	HD: not defined	Skin rash, leukopenia, thrombocytopenia, hemolytic anemia, pancreatitis, URI, headache, diarrhea, nausea, vomiting
	Nateglinide	Initiate at low dose, 60 mg po before each meal	HD: not defined	Cholestatic hepatitis, flu-like symptoms, dizziness
Thiazolidinediones	Pioglitazone	No dose adjustment	No dose adjustment	Black box warning: CHF
	Rosiglitazone	No dose adjustment	No dose adjustment	Black box warning: CHF, MI
Incretin mimetic	Exenatide	Ccr 30–50 ml/min: caution advised Ccr <30 ml/min: avoid	Avoid	Pancreatitis, nephrotoxicity, nausea, vomiting, diarrhea
DPP-4 Inhibitors	Linagliptin	No dose adjustment	No dose adjustment	Pancreatitis, URI, diarrhea, hyperuricemia
	Saxagliptin	Ccr <50 ml/min: 2.5 mg po QD	HD: give dose after dialysis PD: not defined	Lymphopenia, pancreatitis, headache, edema, vomiting, angioedema
	Alogliptin	Ccr 30–59 ml/min: 12.5 mg po QD Ccr <30 ml/min: 6.25 mg po QD	6.25 mg po QD PD: not defined	Skin rash, hepatic failure, headache, URI
	Sitagliptin	Ccr 30–49 ml/min: 50 mg po QD Ccr <30 ml/min: 25 mg po QD	25 mg po QD	Skin rash, acute kidney injury, headache, diarrhea, arthralgia
SGLT2 inhibitors	Canagliflozin	eGFR 49–59 ml/min: 100 mg po QD eGFR 30–44 ml/min: avoid eGFR <30 ml/min: contraindicated	Avoid	Renal impairment, hyperkalemia, pancreatitis, hypotension, UTI, hypermagnesemia, vulvovaginitis, hyperphosphatemia
	Dapagliflozin	eGFR 30–59 ml/min: avoid eGFR <30 ml/min: contraindicated	Avoid	Renal impairment, bladder cancer, orthostatic hypotension, vulvovaginitis, nasopharyngitis, increased serum creatinine
	Empagliflozin	eGFR 30–44 ml/min: avoid eGFR <30 ml/min: contraindicated	Avoid	Orthostatic hypotension, renal impairment, UTI, vulvovaginitis, polyuria

DPP-IV = Dipeptidyl peptidase IV; Ccr = creatinine clearance.

Glycemic monitoring in CKD is complex. Advanced CKD significantly alters the results of HbA1c testing (table 2). Elevated blood urea nitrogen causes the formation of carbamylated hemoglobin and an increased glycosylation rate. Historically, the increase in urea carbamylation falsely elevated the HbA1c measurement; however, newer measures of glycosylated hemoglobin are no longer sub-

ject to this confounding. Other factors that limit the utility of the HbA1c measurement in patients with ESRD or advanced CKD include a shorter erythrocyte life span, iron deficiency anemia, recent transfusion, and erythropoietin treatment, all of which can cause an underestimation of the HbA1c level. Despite these limitations, HbA1c is still considered a reasonable and probably still is the

best measure of chronic glycemic control in this population [45]. In patients who are prone to glycemic variability, glycemic monitoring should be assessed by self-monitoring of plasma glucose plus serial HbA1c measurements.

Oral antihyperglycemic agents including sulfonylureas, meglitinides, biguanides, and alpha-glucosidases are excreted by the kidney, and most of these drugs are contraindicated in advanced CKD. However, some glycemic medications may be used with appropriate dosage adjustments in patients with CKD (table 3). For diabetic patients receiving insulin treatment, it is important to recognize that the kidney clears markedly less insulin when GFR is <20 ml/min. Thus, the insulin requirement is reduced in advanced CKD and ESRD. On the basis of the available evidence, the total insulin dose should be reduced by 25% in patients with an eGFR between 10 and 50 ml/min/1.73 m² and by 50% in patients with an eGFR <10 ml/min. Finally, diabetic pharmacotherapy and adjustments to the regimen in CKD should be individualized based on patient characteristics and lifestyle.

Adjunctive Treatments

Although BP and glycemic control can slow DN progression, additional therapies may also aid to delay the progression of CKD as well as reduce the cardiovascular and overall mortality rate. Adjunctive therapies include lowering LDL cholesterol to <70–100 mg/dl, reducing dietary salt intake to <5 g/day, restricting dietary protein intake to ~0.8 g/kg/day in adults with GFR <30 ml/min/1.73 m², engaging in moderate-intensity exercise, maintaining an optimal body weight, and smoking cessa-

tion. Innovative approaches are needed for successful DN treatment, but the results of many promising recent clinical trials have been disappointing [41, 55, 56]. Further clinical trials will be needed to develop new therapeutic agents in DN.

In summary, there have been reductions in diabetes-related complications in adults with diabetes over the past 30 years, but the overall burden of diabetes-related complications including DN is still increasing because of the large increment in the number of people with type 2 diabetes. DN is a complex disease linking hemodynamic and metabolic pathways with oxidative stress, systemic inflammation, cytokines, and growth factors. The keystones in the disease management are optimal glycemic and BP control. The specific use of agents that block the RAAS is particularly beneficial for slowing renal progression. Lipid-lowering agents, restricted dietary protein and salt intake, weight reduction, smoking cessation, and exercise also confer benefit in this population. Further innovative strategies and treatments that target pathophysiological mechanisms of the disease are needed.

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Disclosure Statement

B.S. has no conflicts of interest to declare. S.G.A. is a member of the Steering Committee and a local participant in the Lilly Pharmaceuticals JAGQ study to test the safety and efficacy of a JAK1/2 inhibitor in overt diabetic nephropathy.

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