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Review

Managing the Course of Diabetic Kidney Disease: From the Old to the New

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ABSTRACT

Diabetic kidney disease (DKD) is a group of chronic kidney diseases that is associated with significant cardiovascular as well as all-cause morbidity and mortality. Although DKD is often progressive in nature, its evolution can be modified by intensive management of glycemia and blood pressure and inhibition of the renin-angiotensin-aldosterone system. This review provides an overview of how multifactorial interventions can provide renal protection and includes a discussion of the nonglycemic effects of incretin-based diabetes therapies (glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase 4 inhibitors) and sodium-glucose cotransporter-2 inhibitors within the kidney in patients with type 2 diabetes.

Mots clés :
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RÉSUMÉ

La néphropathie diabétique (ND) est une forme de néphropathie de longue durée qui est associée à une morbidité et une mortalité cardiovasculaire significative et à une morbidité et une mortalité toutes causes confondues. Bien que la ND soit souvent de nature évolutive, la prise en charge intensive de la glycémie et de la pression artérielle et l'inhibition du système rénine-angiotensine-aldostérone peuvent modifier son évolution. Cette revue donne un aperçu sur la manière dont les interventions multifactorielles peuvent assurer une protection rénale et présente une discussion sur les effets non glycémiques des traitements du diabète à base d'incrétines (agonistes des récepteurs GLP–1 [*glucagon-like peptide–1*] et inhibiteurs de la dipeptidyl peptidase–4) et des inhibiteurs du cotransporteur sodium-glucose de type 2 sur les reins des patients atteints du diabète de type 2.

Case Presentation

A 61-year-old female was diagnosed with type 2 diabetes 14 years ago. Her last glycated hemoglobin (A1C) level was 8.1%, and she is now taking metformin, 1000 mg, twice a day, having recently stopped using a sulfonylurea due to increasingly frequent hypoglycemic events. Her body mass index (BMI) is 31 kg/m^2. She has hypertension, which is being managed with an angiotensin converting enzyme inhibitor (ACEi). There is no history of cardiovascular disease. Her latest blood pressure (BP) reading was 135/82 mm Hg. She has recently developed progressive albuminuria (urine albumin-to-creatinine ratio [UACR]), which increased from

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13.5 to 38.4 mg/mmol over the past 6 months, but has stable renal function (estimated glomerular filtration rate [eGFR] between 75 and 80 mL/min/1.73 m^2).

Introduction

Diabetic kidney disease (DKD) is a serious complication that is observed in both type 1 and type 2 diabetes (1). In this clinical review, using a case presentation, we address clinically relevant questions across the spectrum of interventions that can be utilized to slow the progression of DKD, from glycemic and BP control, inhibition of the renin-angiotensin-aldosterone system (RAAS), as well as newer data utilizing incretin-based diabetes therapies, such as dipeptidyl peptidase 4 inhibitors (DPP-4i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) or sodium-glucose cotransporter-2 (SGLT2) inhibitors. The burden of cardiovascular (CV) disease in those with end-stage renal disease (ESRD) is also discussed.

How prevalent is diabetic kidney disease, and what is the typical phenotype?

DKD occurs in as many as one-quarter to one-half of individuals with diabetes, is the most common cause of ESRD and is associated with an increased risk for CV disease and mortality (2–4). Previously considered a gradual but progressive disease with a spectrum of abnormalities, the prognosis of DKD has significantly evolved over the past few decades. While the prevalence of type 1 diabetes-associated kidney disease has declined, and its progression has slowed due to improved glycemic and BP control (5,6), there has been a surge in type 2 diabetes-associated kidney disease secondary to the growing population of older individuals with longstanding type 2 diabetes and multiple CV comorbidities (6). Observational data suggest that the juxtaposition of age, prolonged dysglycemia and CV risk factors accelerates the decline of the GFR (7).

DKD can manifest across a spectrum of phenotypes. Diabetes can trigger and perpetuate molecular, cellular, structural and functional changes anywhere along the arterial tree, from the larger arteries down to the microvasculature. The classical paradigm of DKD begins with compositional and architectural changes within the microcirculation and glomerular support network (8). The hallmark of early hyperfiltration and microalbuminuria is followed by advancing stages of proteinuria and increasing loss of kidney function, culminating in end-stage kidney failure (9). Nontraditional DKD originates from arteriosclerosis in the larger vessels (10) and is especially common in individuals with diabetes who have poorly managed CV risk factors (6). There is indolent loss of the GFR with minimal proteinuria (6). Although both phenotypes coexist in most cases, there have been many reports of 1 phenotype dominating (10). Staging of DKD is not unlike that of any other kidney disease, where estimation of both the GFR and proteinuria is essential (11). Newer chronic kidney disease classification systems have incorporated both assessments for better prediction of which patients are more likely to progress to ESRD (Figure 1) (12). Although the prevalence of DKD between 1988 and 2014 has been stable at around 30% in adults, mainly those with type 2 diabetes in the United States, the prevalence of albuminuria has declined, and the prevalence of reduced GFR (<60 mL/min/1.73 m^2) has increased (13).

Our patient's A1C level is elevated (8.1%): does intensive glycemic control impact the progression of kidney disease in diabetes?

In patients with type 1 diabetes, after a mean follow up of 6.5 years, intensive glycemic control (mean achieved A1C level of 7.0%) in the Diabetes Control and Complications Trial (DCCT) was associated with a significant reduction in microvascular complications compared to conventional therapy (mean achieved A1C level of 9.0%) (14). There was a 34% relative risk reduction of new-onset microalbuminuria in the primary prevention cohort (no retinopathy at baseline) and decreases of 43% and 56% in new-onset microalbuminuria and macroalbuminuria, respectively, in the secondary prevention cohort (mild retinopathy at baseline) (14). Reductions in rates of albuminuria persisted during long-term observational follow up in the Epidemiology of Diabetes Interventions and Complications (EDIC) cohort (15). Notably, during the DCCT/EDIC, individuals treated with intensive therapy who had developed microalbuminuria were more likely to return to normoalbuminuria (hazard ratio [HR] 1.92) and less likely to develop macroalbuminuria (HR 0.64) (9). There was also a 50% decline in impaired eGFR of lower than 60 mL/min/1.73 m^2 during the DCCT/EDIC in those randomized to intensive glycemic control (16). In summary, achieving an A1C level of 7.0% or lower in type 1 diabetes is associated with a lower likelihood of new or worsening DKD and can lead to regression of markers of DKD in some individuals.

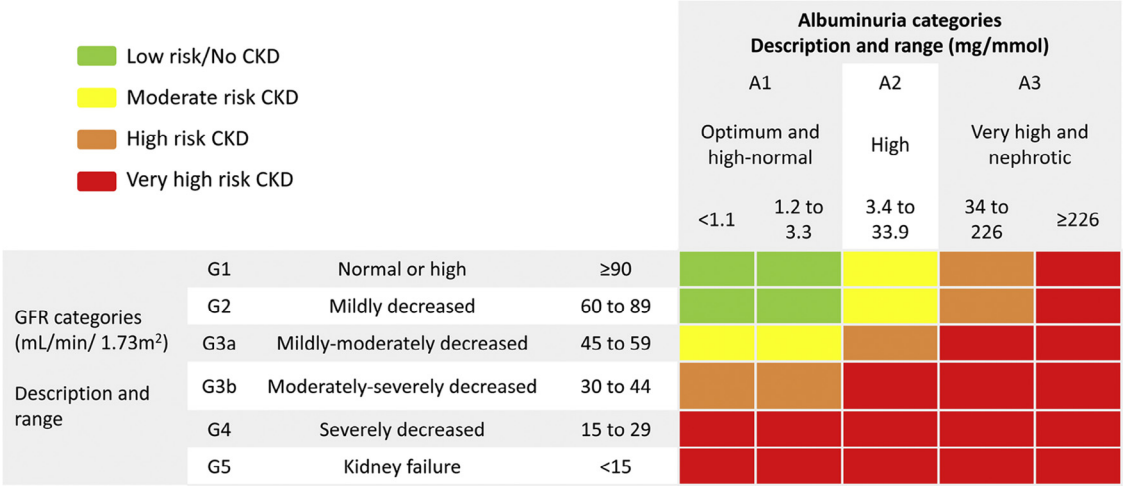

Figure 1. Prognosis of chronic kidney disease by glomerular filtration rate and albuminuria category.
CKD, chronic kidney disease.
Note: Adapted from the KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (11,12).