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Diabetic Kidney Disease

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ABSTRACT

The kidney is probably the most important target of microvascular damage in diabetes. A significant proportion of people with diabetes develop kidney disease because of their disease and/or other comorbidities, including hypertension and age-related kidney loss. The presence and severity of chronic kidney disease (CKD) identifies individuals at increased risk for adverse health outcomes and premature mortality. Therefore, the prevention and treatment of CKD in diabetics is now a central goal of their general care. Intensive care of diabetic patients includes blood sugar and blood pressure control and blockade of the renin-angiotensin-aldosterone system; these approaches reduce the incidence of diabetic kidney disease and slow its progression. In fact, the significant reduction in the incidence of diabetic kidney disease (DKD) over the past 30 years and the improvement in patient prognosis is largely due to improvements in diabetes management. However, there is a need for innovative treatment strategies to prevent and control the progression of DKD. In this review, we summarize what is currently known about the pathogenesis of CKD in patients with diabetes and the key pathways and targets involved in its progression. In addition, we discuss the current evidence that supports the prevention and treatment of DKD and some of the controversies. Finally, we will explore ways to develop new interventions by making urgently needed investments in targeted and focused research.

Keywords: Diabetes; Hypertension; Chronic kidney disease; Albuminuria; SGLT inhibitors

INTRODUCTION

Diabetic kidney disease (DKD) remains by far the most common cause of end-stage renal disease (ESRD) in the United States and most parts of the world.[1,2] The involvement of the kidneys directly and indirectly increases the effects on other organs and increases the morbidity and mortality of diabetics. With the increasing industrialization, increased inactivity and changes in diet and lifestyle, as well as the increasing prevalence of obesity, insulin resistance and type 2 diabetes increases. Since many of the classic diabetic symptoms of type 2

diabetes are absent, unlike type 1 diabetes, the importance of screening methods to identify these patients for kidney involvement is very important.[3,4] Our understanding of the pathogenesis of DKD has also advanced significantly. In addition, several new drugs have undergone clinical trials with some success.

Epidemiology

Diabetes affects 30.3 million people of all ages, which is 9.4 percent of the US population and approximately 149 million people and 10.9 percent of the Chinese population and 415 million worldwide.[5] DKD is the most common cause of end stage renal disease (ESRD) worldwide and is associated with increased morbidity and mortality especially in diabetic patients. Both types of diabetes can lead to CKD and eventually ESRD. However, because the prevalence of type 2 diabetes is much higher than type 1 diabetes, people with ESRD often have type 2 diabetes.[6,7] The overall incidence is approximately 4-17% 20 years after diagnosis and approximately 16% after 30 years. Although the incidence of chronic kidney disease (CKD) in diabetics has decreased in the United States in recent years, the prevalence remains high. In 2018, United States Renal Data System (USRDS) annual data reported that diabetes accounted for 36 percent of chronic diseases in the National Health and Nutrition Examination Survey (NHANES) population from 2013 to 2016, up from 44 percent from 2001 to 2004. However, the total number of DKD patients continued to increase due to the increase in the number of diabetic patients. The number of adults with diabetes over 18 years of age who started treatment for ESRD also increased significantly, from more than 40,000 in 2000 to more than 50,000 in 2014.[8,9] If type 1 diabetics have diabetic nephropathy, they are likely to reach end-stage diabetes. Although the risk of type 2 diabetes after the onset of clinical nephropathy is approximately 20%. Perhaps one of the reasons is that many people with type 2 diabetes die of cardiovascular events before they reach ESRD.[10,11] About 30% of patients with type 2 diabetes who have kidney disease actually have some other kidney disease, but not diabetic nephropathy, as evidenced by the absence of retinopathy and albuminuria.

Definition of diabetic kidney disease

Diabetic kidney disease (also called "chronic kidney disease" due to diabetes (CKD) or diabetic nephropathy) is defined as persistently elevated albuminuria >300 mg/24 h (or >200 µg) in both type 1 and type 2 diabetes or albumin-to-creatinine ratio (ACR) > 300 mg/g, confirmed in at least two of three samples, without evidence of concomitant diabetic retinopathy or other forms of kidney disease.[12] The normal range for albuminuria is 30 mg/g, but values in either range may be associated with an increased risk of kidney and cardiovascular disease. Moderately increased urinary albumin excretion (microalbuminuria) (30-300 mg/g) is widely considered to be a precursor to diabetic nephropathy, indicating both early risk and a target for intervention.[13]

Mechanisms/pathophysiology

DKD has traditionally been considered a microvascular disease grouped together with retinopathy and neuropathy, distinct from macrovascular disease that contributes to coronary artery disease, peripheral vascular disease, and cerebrovascular disease.[14,15] However, each disease can be considered a tissue-specific manifestation of the same pathogenic process, and DKD is a renal manifestation of the same glucose-driven process that occurs elsewhere in the body at sensitive sites. Although all cells in diabetes are exposed to chronically high plasma glucose levels, only some show progressive dysfunction, the best example being the endothelial cells that line blood vessels.[16] In particular, the inability of endothelial cells to regulate their

glucose transport in response to high glucose levels leads to an overwhelming intracellular glucose flux, which triggers the generation of pathogenic mediators that contribute to diabetic complications, including DKD.

Reactive oxygen species

Excessive glucose flux leads to the generation of toxic intermediates, the most important of which are probably reactive oxygen species (ROS).[17,18] Excess glucose production can generate reactive oxygen species in various ways. Increased mitochondrial substrate oxidation and the resulting increased mitochondrial membrane potential lead to overproduction of superoxide. The centrality of ROS in triggering these processes is illustrated by the fact that they can be prevented if hyperglycemia-mediated ROS production is limited.

Pathways of nutrient recognition

Each cell has pathways that recognize nutrient abundance and respond specifically to it to ensure efficient use of the substrate.[19] The best known of these nutrient sensors are rapamycin (mTOR), 5'AMP-activated protein kinase (AMPK) and sirtuins. From a kidney perspective, diabetes directly causes changes in the expression and activity of AMPK, sirtuins, and mTOR37, as well as downstream signaling in cellular homeostasis, including reductions in autophagy, regeneration, mitochondrial biogenesis, and other cytoprotective responses that promote DKD.

Multifactorial pathogenesis of DKD

Only a third of people with type 1 diabetes develop overt nephropathy, while almost all people with type 1 diabetes eventually develop some degree of retinopathy. This suggests that risk factors other than hyperglycemia must be involved in DKD.[20] Pathogenic pathways induced by high glucose levels and maintained in the kidney can be enhanced by a number of different factors. These include several metabolic factors, including fatty acid excess, carbonyl and oxidative stress, and hemodynamic factors, including shear stress from transmitted systemic hypertension, autoregulatory disturbances, hyper perfusion and hypoperfusion, and activation of the renin-angiotensin-aldosterone system (RAAS). These factors themselves do not cause DKD, but rather feed and reinforce the common pathogenic mechanisms in diabetes, which are increased levels of growth factors, vasoactive hormones, cytokines and chemokines in the kidney.

Important structural changes in the glomeruli

Despite the importance of the vascular endothelium in microvascular complications, many researchers suggest that early changes in the glomerulus are critical for the later development of glomerulosclerosis and nephron loss. The most important of these changes may be glomerular podocyte dysfunction.[21-23] They are highly specialized terminally differentiated cells that line the urinary side of the glomerular basement membrane (GBM). Along with glomerular endothelial cells, podocytes are responsible for maintaining the shape and integrity of the GBM, its charge barrier, and the glomerular capillary circuit; all functions that are impaired in diabetic glomeruli. The diabetic environment induces "pathoadaptive" changes in podocytes, including cytoskeletal rearrangements, differentiation, apoptosis and autophagy, manifested by morphological expansion, retraction and flattening (known as loss), decreased motility, increased formation of intercellular tight junctions, glomerular hypertrophy, detachment and disruption.

Glomerular basement membrane thicknening

One of the earliest and most characteristic glomerular changes in diabetes is a homogeneous thickening of the GBM.[24,25] GBM thickening occurs in most patients with diabetes usually within a few years of diagnosis. It is

unclear whether GBM thickening is a marker of podocyte or endothelial dysfunction or a mediator of progressive DKD. Certainly, thickening-related changes in GBM composition, charge, or architecture may contribute to the development of albuminuria. GBM stiffening may also reduce pericapillary wall stretch and compromise the sub podocyte state, facilitating glomerular injury through hemodynamic mechanisms.

Renal tubular dysfunction and fibrogenesis

Diabetes also negatively affects the kidney tubules.[26] At the onset of diabetes, an increased glucose load delivered to the proximal tubule results in cortical tubular maladaptive hypertrophy and hyperplasia with increased glucose transport, which may facilitate glucose reabsorption and reduce glucose waste. However, the consequence of this is that sodium transport in the macula densa is reduced and tubulo-glomerular feedback is activated, leading to increased glomerular pressure and hyperfiltration.[27] Chronic hyperglycemia and other metabolic abnormalities associated with diabetes can cause progressive atrophy of tubular epithelial cells. Such tubular dysfunction results in deficient uptake, transcytosis, and/or lysosomal processing of filtered protein, which also contributes to albuminuria.

Complex histopathology of DKD

The same clinical presentation of DKD can be associated with a heterogeneous set of pathological features, including nodular or diffuse glomerulosclerosis, tubulointerstitial fibrosis, tubular atrophy and renal arteriolar hyalinosis, alone or in combination.[28-30] A histopathologic staging system has been proposed for glomerular lesions. However, its prognostic utility is yet to be determined. Routine renal biopsy is not clinically appropriate in routine practice and DKD remains the clinical diagnosis for most patients with diabetes.

Natural course

The classification of clinical stages of diabetic nephropathy is as follows [31]:

Stage 1: Hyperfiltration

From the onset of diabetes, glomerular filtration and renal blood flow increase, and leads to renal enlargement (renomegaly). Urinary albumin excretion rate (UAE) is usually less than 30 mg in 24 hours and blood pressure is also normal. The first pathologic finding is GBM thickening. If the initial glomerular filtration rate (GFR) is more than 150 ml per minute, it increases the possibility of diabetic nephropathy.

Stage II: Microalbuminuria

As kidney disease progresses, UAE also develops. This is also called latent or subclinical nephropathy. A standard strip test is often negative at this stage. Changes in the degree of albuminuria over time are associated with different risks of renal decline, so that patients with microalbuminuria with increased, persistent, or decreased albumin burden are at very high, moderate, and low risk of GFR decline. In type 1 diabetes, when albuminuria increases, the incidence of other microvascular complications, such as retinopathy and neuropathy, also increases. Hyperlipidemia, age, duration of diabetes are also risk factors for microalbuminuria. Diagnosis at this stage is a very good chance to avoid progression to clinical nephropathy or even back to normoalbuminuric. However, without treatment, the risk of developing clinical nephropathy is high in type 1 diabetes after 10-15 years (more than 75%) and in type 2 diabetes after 15-20 years (20-40%).

Stage III: Macroalbuminuria

This stage is also called clinical nephropathy, which appears about 10-20 years after the onset of diabetes (about 5-10 years after the onset of microalbuminuria). Coronary artery disease and cerebrovascular events also clearly increase in this stage compared to the previous stage. About 75 percent of patients at this stage have high blood pressure. Controlling blood pressure in type 2 diabetics with a history of hypertension is more difficult. At this stage, a standard dipstick is positive for proteinuria, and urinary albumin excretion is greater than 300 mg in 24 hours. After that, the GFR decreases, about 10-12 ml per year. When clinical nephropathy appears and in the absence of therapeutic measures, kidney function gradually deteriorates and proteinuria increases, which can reach the nephrotic range. Diabetic retinopathy is very useful in confirming the diagnosis of diabetic nephropathy. Hypertension and proteinuria independently lead to decreased GFR and progression to ESRD. 20% of patients with type 2 diabetes before the development of clinical nephropathy and 40% of patients with clinical nephropathy have renal vascular disease. Tubulointerstitial fibrosis also begins at this stage, and if its extent and severity are greater, kidney damage and prognosis are worse.

Stage IV

End stage kidney disease Almost 20-30 years after the onset of diabetes, about 10 years after the onset of clinical nephropathy, the patient reaches this stage.[32] The risk with type 1 diabetes is higher than type 2 diabetes. However, the prevalence of type 2 diabetes is 9 times higher than type 1 diabetes, so most diabetics with ESRD have type 2 diabetes. Under these conditions, the death rate of diabetic patients is higher than that of non-diabetic patients.[33-35] In addition, cardiovascular diseases are higher in these patients. At this stage, the incidence of diabetic foot ulcers is higher, sometimes up to 25%.[36,37] In the UKPDS report, the annual chance of diagnosis from diabetes to microalbuminuria, from microalbuminuria to overt nephropathy, and from overt nephropathy to elevated serum creatinine or conversion to renal replacement therapy are 2%, 2.8%, and 2.3%, respectively.

Risk factors for DKD

Several different factors contribute to the development of CKD in diabetics. Some of these factors, including hyperglycemia, hypertension, weight gain, and dyslipidemia, are potentially modifiable with optimized diabetes treatment.[38] In addition, extensive clinical data show that intensive diabetes management significantly reduces the incidence of albuminuria, renal failure as well as ESRD. Indeed, the significant reduction in the incidence of CKD over the past 30 years is largely due to improvements in diabetes management.

Poor glycemic control

The most important risk factor for CKD is hyperglycemia. Although there are structural similarities to other kidney diseases, the DKD phenotype is essentially only observed in the presence of elevated glucose levels.[39, 40] A definitive prospective clinical study by Jean Pirart and colleagues in Belgium showed unequivocally that the degree and duration of hyperglycemia were associated with microvascular complications, including CKD. Subsequent randomized controlled trials have confirmed this causal relationship in both type 1 and type 2 diabetes. However, although normal glucose levels, such as glycated hemoglobin (HbA1c), are associated with microalbuminuria, it is also clear that many patients with poor blood glucose levels do not develop kidney complications, while others do despite intensive interventions and dedicated control measures. Previous episodes of poor glucose balance, even before diagnosis, can also have a long-term effect in the kidney, and therefore DKD risk may not be represented by current or recent HbA1c levels. This phenomenon was known as

"metabolic memory", "metabolic karma" or the "inheritance effect".[41] The physiological mechanism or mechanisms responsible for metabolic karma remain poorly defined, but may involve epigenetic programming, remodeling, and permanent post-translational modifications such as enhanced glucose end products. Understanding the molecular basis of the metabolic inheritance of diabetes will certainly add new targets for intervention to reduce the burden of CKD in diabetics.

High blood pressure

Increased blood pressure is a major risk factor for CKD in both type 1 and type 2 diabetes. In people with type 1 diabetes, blood pressure levels are usually normal at diagnosis, but increase near microalbuminuria.[42] In type 2 diabetes, other factors influence the appearance and severity of hypertension, which can precede or follow chronic kidney disease for several years. The importance of hypertension in the pathogenesis of renal injury can be partially explained by the loss of renal autoregulation in diabetes, in which systemic pressure is transmitted directly to the vulnerable glomerular capillaries. Thus, there is no specific threshold above which the specific risk of CKD can be expressed or below which the therapeutic effect of blood pressure control on the development of albuminuria can be ignored in diabetic patients.

Lipid abnormalities

Dyslipidemia is another important risk factor for the development of chronic diseases of diabetes.[43] Specifically, high levels of triglycerides, low-density lipoprotein cholesterol, apolipoprotein-B-100, or low high-density lipoprotein (HDL) cholesterol are independently associated with the development of CKD in both type 1 and type 2 diabetes. However, conventional lipid and lipoprotein measurements do not fully account for the complex lipid and lipoprotein changes associated with diabetes and/or CKD. For example, not only can HDL lose its vascular protective, antioxidant, and anti-inflammatory properties in CKD, but dysfunctional HDL can also be directly pathogenic. Lipidomics has been used to create a "lipid fingerprint" linked to diabetes complications. However, it remains unclear which lipids or lipoproteins are most important in the pathogenesis of diabetic CKD.

Insulin resistance

Insulin resistance is also independently associated with CKD, in addition to indirect associations with glucose, blood pressure, body weight, and lipid regulation.[44] Insulin-sensitizing measures (eg, thiazolidinedione therapy, exercise, and weight loss) reduce albuminuria in addition to metabolic control. Decreased insulin sensitivity also causes changes in glucose metabolism in kidney cells. At the same time, increased insulin signaling due to compensatory hyperinsulinemia in the setting of selective insulin resistance can contribute to vasoreactivity, angiogenesis, fibrogenesis and other pathways involved in progressive kidney disease and atherogenesis.

Obesity

CKD occurs more frequently and progresses more rapidly in obese diabetics than in their normal-weight counterparts.[45] This is one of the main reasons why the cumulative incidence of CKD is higher in type 2 diabetes than in type 1 diabetes. Obesity adversely affects key risk factors associated with CKD, including lipid, blood pressure, and glucose balance, and promotes insulin resistance. Obesity also has direct effects on the kidney, including changes in intraglomerular hemodynamics, increased sympathetic activity, hypertension, systemic inflammation, endothelial dysfunction, altered expression of growth factors, and renal compression

associated with visceral obesity. Indeed, even in the absence of diabetes, obesity can be associated with increased albuminuria and its severity, and obesity-related glomerulopathy has been widely described.

Hepatitis C virus (HCV) infection and CKD

HCV infection is more common among CKD patients than in the general population.[46,47] According to recent research, CKD patients with HCV infection had a faster loss of renal function and a higher chance of developing ESRD. The important question of whether treating to achieve a sustained virologic response, defined as an undetectable viral load 12 weeks after completion of treatment (SVR12), would slow the rate of decline in GFR was raised by a study which demonstrated that HCV-infected patients with CKD had an increased mortality and an accelerated rate of progression to ESRD.[48] Most patients with mixed cryoglobulinemia and many histological types of glomerular damage, including membranoproliferative and membranous GN, have been linked to HCV infection as the underlying cause of these conditions.

Associations of CKD and cardio-vascular disease (CVD)

In recent years, an increasing number of studies have shown that patients with chronic kidney disease have an exceptionally high risk of cardiovascular disease.[49] In fact, death from cardiovascular causes is the most important competing outcome for the development of ESRD in patients with CKD. In patients with stage 3 CKD (eGFR ≤ 60 ml/min/1.73 m2), the risk of death is more than 10 times greater than the risk of progression to ESRD. In part, the high risk of death is due to the large difference in the number of patients with earlier-stage CKD compared to those with ESRD.[50] For the relatively few patients who later develop ESRD, the prognosis is poor, with an average five-year survival rate of less than 40%, largely due to cardiovascular morbidity and mortality.[51] Decreased eGFR and increased albuminuria have been identified as independent risk factors for all-cause and CVD mortality in the general population. A meta-analysis of cohort studies in the general population showed that hazard ratios (HRs) for CVD mortality, defined as MI mortality, heart failure, stroke, or sudden death, increased progressively with decreasing eGFR.[52] When it was less than 60 mL/min/1.73 m2, the CVD mortality rate without albuminuria increased from 1.52 in patients with eGFR of 45-59 mL/min/1.73 m2 to 13.51 in patients with eGFR was 15-29 mL/min per 1.73 m2. Albuminuria above 10 mg/g without a decrease in eGFR has also been found to be associated with a progressive increase in CVD mortality.[53,54] When both occurred together, decreased eGFR and albuminuria were multiply associated with CV death. After the establishment of CKD as a strong predictor of CVD, clinical guidelines, including those of the American Heart Association, began to accept the inclusion of patients with CKD in recommendations as the highest risk population for CVD disease prevention, detection, and treatment.[55]

ESRD in diabetes

Globally, 80% of ESRD cases are caused by diabetes, hypertension or a combination of these.[56] Compared to adults without diabetes, the incidence of ESRD is up to 10 times higher in diabetics. However, only a limited number of patients with CKD associated with diabetes ever receive renal replacement therapy, as 78% of these individuals live in low- and middle-income countries with limited resources, coverage, and access to dialysis and kidney transplantation. The proportion of diabetes related ESRD varies greatly in different parts of the world. In 2014, between 5% and 66% of new cases of ESRD were mainly due to diabetes.[57-59] The highest proportion was in Singapore, Malaysia and the Jalisco region of Mexico, and the lowest in Norway, Romania and Iceland. In most countries at the upper end of this distribution, the incidence of diabetes related ESRD has

increased dramatically over the past decade. Between 2001 and 2015, the highest growth was in Thailand at 1,448%, Russia at 981% and the Philippines at 378%.[60] Because these figures are reported for the entire state-based population, they primarily reflect the increasing prevalence of diabetes in those populations, partly due to a shift in the burden of disease from infections to chronic lifestyle diseases and increased life expectancy. The prevalence of treated ESRD was highest, ranging from 1568 to 3219 per million inhabitants, in some of the Asian countries such as Japan, Singapore, and in the United States.[60] Although the incidence of treated ESRD has been fairly stable or declining in many countries in recent years, the incidence has steadily increased in all 32 countries that reported data between 2001 and 2014. In the United States, 44% of new cases of ESRD are due to diabetes (either type 1 or type 2), highest in non-Hispanic blacks and lowest in non-Hispanic whites.[61-63] Detailed quantitative data on the trend of diabetes-related ESRD and its association with other complications of diabetes in the United States are presented in an analysis of several nationally representative databases (NHIS, National Hospital Discharge Survey, US Renal Data System, and National Vital Statistics System) in the years 1990-2010. Deaths from heart attack, stroke, amputation, end-stage disease and hypoglycemia were reduced in the diabetic population (primarily type 2 diabetes). The greatest reduction is for cardiovascular events and the least for ESRD. In the 1990s, the incidence of diabetes related ESRD was low because CVD morbidity and mortality were important competing events. The decline in these competing causes over the next decade allowed people with diabetes to live long enough to develop ESRD, which explains why the decline in ESRD is smaller. However, the study found a statistically significant decrease in diabetes related ESRD in all age groups after 2000, consistent with significant progress in the adoption of reno-protective therapies nationwide.

Screening

Annual screening of all diabetic patients is recommended to detect abnormal and/or variable levels of albuminuria and renal function (ie, eGFR) so that early renoprotective therapy can be initiated.[64] Early morning spot urine is sufficient for screening and monitoring and is convenient for the patient. To account for the large intraday variability (30-40%), 2 of the 3 spot urine samples must be collected within 3-6 months to confirm the diagnosis. A 24-hour urine collection has been considered the gold standard for evaluating albuminuria and can provide additional information on sodium and protein intake, but a complete urine collection is often difficult for the patient, so this method is usually limited to patients with established diabetic kidney disease. It should be noted that urinary albumin excretion may increase independently of kidney disease due to factors such as heavy exercise within 24 hours, severe UTI, menstruation, heart failure, and marked hyperglycemia.[65] Another clinical variable assessed in diabetic kidney disease screening is eGFR using creatinine-based formulas such as the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The "natural" course of untreated diabetic nephropathy shows a continuous annual decline in eGFR of 2-20 ml/min/1.73 m2 (average 12 ml/min/1.73 m2), but effective treatment focuses on glycemic, blood pressure control, renin-angiotensin system (RAS) inhibition, lowering blood cholesterol and improving lifestyle factors can limit progression to 2-5 mL/min/1.73 m2 per year, indicating the importance of screening and interventions.

Management

Treatment of hypertension:

Observational studies in the general population have shown a strong and linear association between blood pressure and cardiovascular disease risk, with the risk of cardiovascular events doubling for every 20/10 mmHg increase in systolic/diastolic blood pressure above 115/75 mmHg.[66] In addition to directly affecting CV risk, hypertension contributes to kidney damage in diabetes and albuminuria; therefore, it is an important target for management. According to the Kidney Disease Outcomes Initiative clinical practice guidelines for blood pressure control in CKD, a goal of less than 140/90 mmHg was recommended in those diabetic patients without significant albuminuria (30 mL/min/1.73 m2).

RAAS inhibition and albuminuria

By opposing the renin-angiotensin-aldosterone system (RAAS); angiotensin-converting enzyme inhibitors (ACEs) and angiotensin receptor blockers lower blood pressure and albuminuria.[67] The Irbesartan Diabetic Nephropathy Trial (IDNT) showed that irbesartan protects against the progression of nephropathy in patients with type 2 diabetes regardless of the drop in blood pressure.[68] The Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) in diabetic and non-diabetic patients showed that although the combination of ramipril and telmisartan reduced proteinuria compared with either agent alone, the time to initiation of dialysis was not delayed.[69,70] There are enough studies to compare the effectiveness of ACE inhibitors and angiotensin receptor blockers in this situation. These results are already a cornerstone of the treatment of diabetic nephropathy and can be used to support the routine use of RAAS inhibitors in the treatment of patients with type 2 diabetes, regardless of baseline albuminuria.

Treatment of hyperglycemia

Hyperglycemia, a hallmark of diabetes, is an important therapeutic goal in all diabetic patients. As shown in important studies such as Epidemiology of Diabetes Interventions and Complications (EDIC) and UKPDS, tight glycemic control reduces the risk of microvascular complications, including nephropathy, in patients with type 1 and type 2 diabetes.[71] Current evidence supports therapy with a target HbA1c of 7.0% to slow the onset of microvascular complications, including nephropathy. Of note, no prospective randomized clinical trial has evaluated the effect of glycemic control on health outcomes in patients with CKD stages 3-5. Because patients with CKD are more prone to hypoglycemia than patients with preserved eGFR, it remains unclear whether the same HbA1c target is optimal for this population.

Metformin

Metformin remains the first-line antihyperglycemic treatment for most patients with T2D because of its low cost, high efficacy, and low risk of hypoglycemia.[72] In addition, it has weight- and lipid-lowering properties, as well as beneficial effects on CV mortality. Metformin is mainly excreted by the kidneys. Despite limited data, the increased risk of lactic acidosis in patients with lower eGFR has limited its use to patients with eGFR >30 mL/min/1.73 m2.

Inhibitors of sodium-glucose cotransporter-2 (SGLT-2i)

SGLT2i is now a widely used antihyperglycemic drug for type 2 diabetes.[73] Several CV outcome studies, including the Empagliflozin Cardiovascular Outcome Event (EMPA-REG OUTOME) study and the Canagliflozin Cardiovascular Assessment Study (CANVAS), have shown that SGLT2i provides significant renal benefits in addition to CV benefits.[74] The CANVAS Renal study reported a corresponding 40% reduction

in the renal composite outcome (persistent decline in eGFR, need for renal replacement therapy, or death from renal causes).[75,76] SGLT2i reduces renal glucose reabsorption, resulting in osmotic diuresis and plasma volume depletion. Approximately one-third of SGLT2i-treated patients experience a reversible decline in eGFR of more than 10%. Although they are relatively weak glucose-lowering agents, they have the added benefit of lowering blood pressure and weight and do not cause hypoglycemia. Possible side effects include an increased risk of fluid depletion, genital and urinary tract infections, perineal necrotizing fasciitis, and euglycemic ketoacidosis.

Glucagon-like peptide-1 receptor agonists

In T2D, GLP-1 RA represents a family of injectable antihyperglycemic drugs.[77] In particular, liraglutide, semaglutide and dulaglutide have shown significant CV and renal benefits in large CV outcome trials, particularly in patients with established CVD or at high risk. In the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial, liraglutide reduced cardiovascular death by 22% and all-cause death by 15% compared to placebo.[78] Long-term follow-up data in patients with DKD also showed a 22% reduction in combined nephritis, mainly due to a lower incidence of severely elevated albuminuria. Several GLP-1 receptor agonists, including liraglutide, semaglutide have low renal clearance and hence are safer to use even in patients with advanced diabetic kidney disease. Major guidelines, including those of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes, now recommend the use of GLP-1 RAs to reduce cardiovascular risk in T2D, regardless of glucose control. In clinical practice, the most common side effects of GLP-1 RA are gastrointestinal symptoms, injection site reactions, and increased heart rate. GLP-1 RAs should also be avoided in patients at risk of developing medullary thyroid tumors or with a history of acute pancreatitis.

Treatment of dyslipidemia

Dyslipidemia, a highly modifiable risk factor for CV events in the general population, is common in patients with diabetes and CKD (79). Data showing a reduction in cardiovascular events due to low-density lipoprotein (LDL) cholesterol lowering by in CKD patients was originally derived from multiple post hoc analysis of large randomized controlled trials with enough CKD patients. It used to be recommended for diabetics and people with CKD stages 1-4, with statins as first-line agents, to achieve serum LDL cholesterol levels below 100 mg/dL or optionally below 70 mg/dL. However, some targets of LDL cholesterol treatment were omitted from the recent recommendations for lipid management in patients with CKD in the 2013 Clinical Practice Global Outcomes for the Improvement of Kidney Disease. These recommendations are consistent with recent prevention guidelines from the American Heart Association and the American College of Cardiology, which recommended that the decision to initiate cholesterol-lowering therapy (especially statin therapy) be based on the absolute risk of coronary events.[80] Thus, statin therapy should be considered in almost all patients with diabetes and chronic diseases due to their high CVD risk and the pleiotropic effects of statins. It is not clear whether patients using statins should stop using them when starting dialysis.

Lifestyle changes

All patients with diabetic nephropathy should receive recommendations for lifestyle changes that can reduce their risk of progression and development of cardiovascular disease.[81] For patients who smoke, tobacco cessation is essential, as it not only significantly and directly reduces the risk of cardiovascular disease but can also slow the progression of early diabetic nephropathy. In addition to following a diabetic diet, patients with

nephropathy have traditionally been advised to limit salt and protein intake. Reducing salt intake by 8.5 g per day has been shown to lower blood pressure by 7/3 mmHg, similar to monotherapy.[82] However, it should be noted that a recent prospective observational study in patients with type 1 diabetes who did not have ESRD showed that the relationship between salt intake and mortality as assessed by urinary sodium excretion is non-linear, with decreased survival in patients with the highest and lowest levels of excretion regardless of kidney disease. Clinical trials are needed to assess the effect of dietary salt restriction on mortality in this setting. Dietary protein restriction may improve eGFR in patients with diabetic kidney disease, although the quality of the evidence is not high. Finally, combining lifestyle changes with intensive treatment can significantly reduce the risk of cardiovascular disease and prevent the progression of microvascular disease.

Management of CVD

Prevention and treatment of diabetic nephropathy and reduction of risk of cardiovascular diseases Considering the high mortality rate of patients with diabetic nephropathy, primary prevention of its development and efforts to prevent the progression of the disease after detection are extremely important (83). Unfortunately, CKD is often unrecognized by patients and providers. In addition, patients diagnosed with CKD are less likely to achieve an adequate change in CVD risk factor than the general population. The key to improving outcomes in this vulnerable patient population is simply to increase awareness of these issues and intervene as early as possible.

Future recommendations

Despite significant advances in the pharmacological management of patients with diabetes, available DKD therapies can slow the decline in GFR, and a significant CV risk remains. Research into potential new therapeutic targets for diabetic kidney disease is currently active and brings a lot of expectation and optimism to this field. New targets for therapeutic interventions include drugs that inhibit the formation and function of Advanced Glycation End Products (AGEs) or AGE receptors, drugs that target oxidative stress, inflammatory cytokines or fibrosis. The role of microRNAs in the pathogenesis of DKD is an emerging field and may also provide new therapeutic approaches. Cell therapies for regenerating blood vessels within the kidney are in the early stages of clinical trials. New insights into the molecular mechanisms underlying the origin and progression of DKD are emerging from extensive genetic and molecular studies in experimental models and humans.

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