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Actual Problems of Diabetic Nephropathy, Risk Factors, Stages, Progression, Mechanism, Diagnosis and Management

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Abstract: With the growing awareness that chronic kidney disease (CKD) is an international health problem, Kidney Disease: Improving Global Outcomes (KDIGO) was established in 2003 with its stated mission to "improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines." The prevalence of diabetes around the world has reached epidemic proportions. The International Diabetes Federation estimated that 537 million people were living with diabetes in 2021. This number is expected to increase to 784 million by 2045. It has been estimated that 40% or more of people with diabetes will develop CKD, including a significant number who will develop kidney failure requiring dialysis and transplantation.

Diabetic kidney disease (DKD) is a major public health problem characterized by elevated urine albumin excretion or reduced glomerular filtration rate or both. The pathophysiology of DKD involves various pathways like hemodynamic, metabolic, and inflammatory pathways. Increase in reactive oxygen species formation induced by hyperglycemia through activation of electron transport chain considered as the initiators in the development of diabetes complications. Prevalence of DKD is raising continuously with disparate growth in low to middle-income countries and under-recognized as a global burden of disease. DKD imposes an enormous humanistic, economic, and societal burden. DKD in the initial stage is often undiagnosed until the manifestations of serious complications. The major hurdle in the early diagnosis is limited knowledge, unroutine screening. Timely diagnosis and appropriate interventions are the best approaches to deal with this catastrophic condition. Early diagnosis can have lifetime benefits by controlling the progression of the disease, increasing life expectancy, decreasing the humanistic and economic burden. Even after all these benefits; DKD cases are diagnosed when the condition worsens. Non-availability of potential diagnostic biomarkers is the main barrier to the early diagnosis of DKD. The present review highlights the worldwide prevalence, risk factors, and potential biomarkers for the early detection of DKD.

Introduction

Patients with kidney disease may have a variety of different clinical presentations. Some have symptoms that are directly referable to the kidney (gross hematuria, flank pain) or to extrarenal symptoms (edema, hypertension, signs of uremia). Many patients, however, are asymptomatic and are noted on routine examination to have an elevated serum creatinine concentration or an abnormal urinalysis.

Once kidney disease is discovered, the presence or degree of kidney function impairment, kidney damage, and rapidity of progression are assessed, and the underlying disorder is diagnosed. Although the history and physical examination can be helpful, the most useful information is initially obtained

from estimation of the glomerular filtration rate (GFR), assessment of albuminuria (or proteinuria), and examination of the urinary sediment.

The kidney performs many functions, including elimination of nitrogenous wastes; regulation of fluid, electrolyte, acid-base, and mineral balance; control of blood pressure; and synthesis and secretion of erythropoietin and other hormones. The GFR is considered the best overall measure of the kidney's ability to carry out these various functions, and therefore estimation of the GFR is used clinically to assess the degree of kidney impairment and to follow the course of the disease. However, the GFR provides no information on the cause of the kidney disease. This is achieved by the urinalysis, measurement of urinary protein excretion, kidney imaging, and, if necessary, kidney biopsy.[3-13]

Risk Factors

1. Increased albuminuria

Increase excretion of albumin in the urine is a major risk factor for the development and progression of kidney disease in people living with diabetes. It is characterized by increased excretion of albumin/g creatinine in the urine referred to as microalbuminuria (30–300 mg/g) or macroalbuminuria (>300 mg/g).

2. Hyperglycemia

Hyperglycemia is considered as one of the most prominent and independent risk factors of DKD. It increases the worsening of renal function by altering the antioxidant system which leads to the increased formation of advanced glycation end products. Polyol pathway activation is also postulated in the pathogenesis of DKD. Variability in glycated hemoglobin (HbA1c) is associated with the development and progression of nephropathy in both type 1 DM patients and T2DM patients. A similar finding was reported by the Renal Insufficiency And Cardiovascular Events (RIACE) an Italian multicenter study. Evidence from randomised controlled trials found beneficial effects of intensive glucose control in the delayed onset as well as in preventing the progression of albuminuria in T2DM patients.

3. Hypertension

Hypertension is a pivotal risk factor for diabetic nephropathy. Hypertension is significantly associated with the development of diabetic nephropathy as confirmed by a recent meta-analysis. In children with CKD hypertension is associated with cardiovascular disease. Hypertensive patients are at higher risk of developing diabetic nephropathy as compared to non-hypertensive patients with an odds ratio of 1.67 (95% CI: 13.1–2.14). This was further confirmed by a population-based prospective study from china which states that hypertension control can reduce the incidence of end-stage kidney failure by 23%.

4. Dyslipidemia

Dyslipidemia plays an important role in the development and progression of DKD. The impact of dyslipidemia on renal function impairment was described by the "lipid nephrotoxicity hypothesis". In people with diabetes, dyslipidemia is characterized by a decrease in high-density lipoprotein, and an increase in triglycerides, low-density lipoprotein, and very-low-density lipoprotein. Dyslipidemia has a role in the development of DKD by causing apoptosis of podocytes, macrophage infiltration, and excessive production of extracellular matrix. Hyperglycemia and insulin resistance could aggravate dyslipidemia in DKD patients. Evidence from epidemiological studies suggested a positive correlation between dyslipidemia and diabetic nephropathy.

An epidemiological study on 581 T2DM patients investigating the association between lipoprotein and DKD found a positive association. Lipoprotein levels were found to be directly correlated with the prevalence of DKD. A Nigerian study assessing the relationship between microalbuminuria and T2DM found a positive correlation between urine albumin creatinine ratio (UACR) and triglycerides ($p < 0.001$). LDL/HDL ratio was the independent predictor of microalbuminuria.[1]

5. Obesity

Evidence suggests a strong association between obesity and DKD.

The mechanism by which obesity leads to DKD is not clear but it is presumed that obesity leads to glomerular injury, glomerular hypertrophy, and proteinuria. A Chinese study on 264 patients with confirmed DKD based on renal biopsy found obesity as a risk factor in the development of nephropathy. Besides, a secondary analysis of Look AHEAD randomised clinical trial suggests weight loss as an adjunctive treatment to delay the progression of diabetic nephropathy in obese patients.

6. Smoking

Smoking is considered as an independent risk factor in the development and progression of diabetic nephropathy. The pathogenic role of smoking in the development of diabetic nephropathy is multifactorial including oxidative stress, hyperlipidemia, deposition of advanced end glycation products, and glomerulosclerosis. Evidence form a Finnish diabetic nephropathy study on 3613 type 1 DM patients found a higher risk of albuminuria and end-stage renal disease in smokers as compared to non-smokers. The risk of diabetic nephropathy was found to be increased with the dose of smoking. This was also confirmed by a recent meta-analysis based on the pooling of nine cohort studies which concludes that smoker T2DM patients are at an increased risk of developing diabetic nephropathy. [14-29]

7. Genes, such as ACE, APOC1, GREM1, UNC13B, ALR2, APOE, CARS, CPVL/CHN2, eNOS, EPO, FRMD3, HSPG2, and VEGF, are identified for the hereditary reasons of DN. ELMO1, CCR5, and CNDP1 were identified to be the reason for ND in a subgroup of T2DM Asian subjects. Polymorphic genes of ADIPOQ, PAI-1, TGFβ1, and PPARγ also have been studied and shown their crucial role in developing DN. High levels of HbA1C, proteinuria, systolic blood pressure, and habits increase the risk of DN in DM patients.

Stages of Diabetic Kidney Disease

Stages of diabetic nephropathy DKD is a chronic complication of both type 1 diabetes mellitus (DM) (beta cell damage, absolute lack of insulin) and type 2 DM (insulin resistance and/or decreased secretion of insulin).

There are five stages in the development of diabetic nephropathy.

Stage I, GFR is either normal or increased; lasts around 5 years from the onset of the diabetes. The size of the kidneys is increased by nearly 20% and renal plasma flow is increased by 10%-15%, but without albuminuria or hypertension.

Stage II, starts more or less 2 years after the onset of the disease with thickening of basement membrane and mesangial proliferation with normalization of GFR but without clinical signs of the disease. Many patients continue in this stage for life. However, stage III, represents the first clinically detectable sign of glomerular damage and microalbuminuria (albumin 30-300 mg/day). It usually occurs 5 to 10 years after the onset of the disease with or without hypertension. Approximately 40% of patients reach this stage.

Stage IV, is the stage of CKD with irreversible proteinuria (>300 mg/day), decreased GFR below 60 mL/min/1.73 m2, and sustained hypertension.

Stage V, is defined when ESKD with GFR <15 mL/min/1.73 m2 is detected. Nearly 50% of patients will need renal replacement therapy in the form of peritoneal dialysis, hemodialysis or kidney transplantation [30].

Progression of Diabetic Nephropathy

As not every diabetic patient advance to macroalbuminuria, microalbuminuria serves to diagnose DN. Normal albumin levels may be regressed in some patients. Type 2 DM patients show high variability in DN progression. The variability is evident as DN is mostly considered as a secondary disorder of DM and onset date is often under-diagnosed.[31] Recent research showed 38% of patients

develop microalbuminuria and 29% showed decreased GFR after 15 years of follow-up. Additionally, they reported a progression of 2.8% from microalbuminuria and 2.3% from GFR to ESRD [32]. mentioned that the progression of renal disease was gradually increasing at 17.3%, 24.9%, and 24.9% for the first 5 years, 10 years, and 15 years from the date of diagnosis.

Mechanisms of kidney damage in diabetes

Glomerular hemodynamic disturbances

Hyperglycemia induces glomerular hyperfiltration and hypertension, hemodynamic mechanisms that have long been recognized to initiate and propagate kidney damage in diabetes. Glomerular hyperfiltration is exacerbated by high levels of amino acids, for example, after protein overfeeding, or with hormonal changes associated with poor glycemic control, for example, a high level of glucagon. These circulating mediators of glomerular hyperfiltration primarily act by increasing perfusion through afferent arteriole dilation. In addition, activation of the renin angiotensin system is a key local trigger for glomerular hyperfiltration. Angiotensin II production within the kidney constricts the efferent arteriole, and thereby, contributes to higher glomerular pressure. Angiotensin II stimulates expression of proinflammatory and profibrotic mediators via this barotrauma and also by direct cellular effects.

The sodium-glucose cotransporter-2 (SGLT2) is now recognized as another important modulator of glomerular hemodynamics. It is expressed on the luminal surface of epithelial cells in the proximal convoluted tubule and is responsible for 90% of filtered glucose reabsorption. In hyperglycemic conditions, SGLT2 expression and activity increase as an adaptation to reclaim glucose from the urine, but there is a maladaptive consequence of worsening hyperglycemia. Therapeutically, SGLT2 inhibition lowers blood glucose by decreasing glucose reabsorption at the proximal tubule resulting in glucosuria. In addition, SGLT2 inhibitors restore tubuloglomerular feedback by increasing distal delivery of sodium chloride to the macula densa, where solute reabsorption generates adenosine as a by-product of adenosine triphosphate utilization. Adenosine acts in a paracrine manner to enhance afferent arteriolar vasoconstriction, suppress renin release from juxtaglomerular cells, and perhaps reduce efferent arteriolar constriction. The relative balance between increasing afferent and decreasing efferent arteriolar constriction in response to SGLT2 inhibition may vary by diabetes type and age. In physiological studies of humans with normal or high GFR, younger people with T1D demonstrated afferent arteriolar constriction, whereas older people with T2D had evidence of efferent arteriolar dilation. Irrespective of the precise vasoregulatory mechanisms, on the whole, restoration of tubuloglomerular feedback reduces glomerular hypertension and, thereby, hyperfiltration.

Inflammation and fibrosis

Hyperglycemia prompts a series of intracellular processes that promote kidney damage via inflammation and fibrosis. Altered intracellular glucose metabolism generates advanced glycation end products (AGEs), reactive oxygen species, and activation of protein kinase C and the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathways. Podocytes exposed to AGE increase nuclear factor κB–associated upregulation of messenger RNA expression for a variety of proinflammatory mediators by as much as 25-fold. In podocytes and endothelial cells, AGEs bind to the receptor for AGE (RAGE), to produce inflammation via the nucleotide-binding oligomerization domain–like receptor pyrin domain containing 3 inflammasome. Together, nuclear factor κB and nucleotide-binding oligomerization domain–like receptor pyrin domain containing 3 induce expression and activation of the interleukins (IL), IL-1β and IL-18, respectively.Moreover, AGEs increase expression of serum amyloid A, another RAGE activator, that perpetuates a feed-forward cycle of inflammatory gene expression .These intracellular signals lead to ongoing release of proinflammatory mediators, profibrotic factors, and immune cell recruitment.

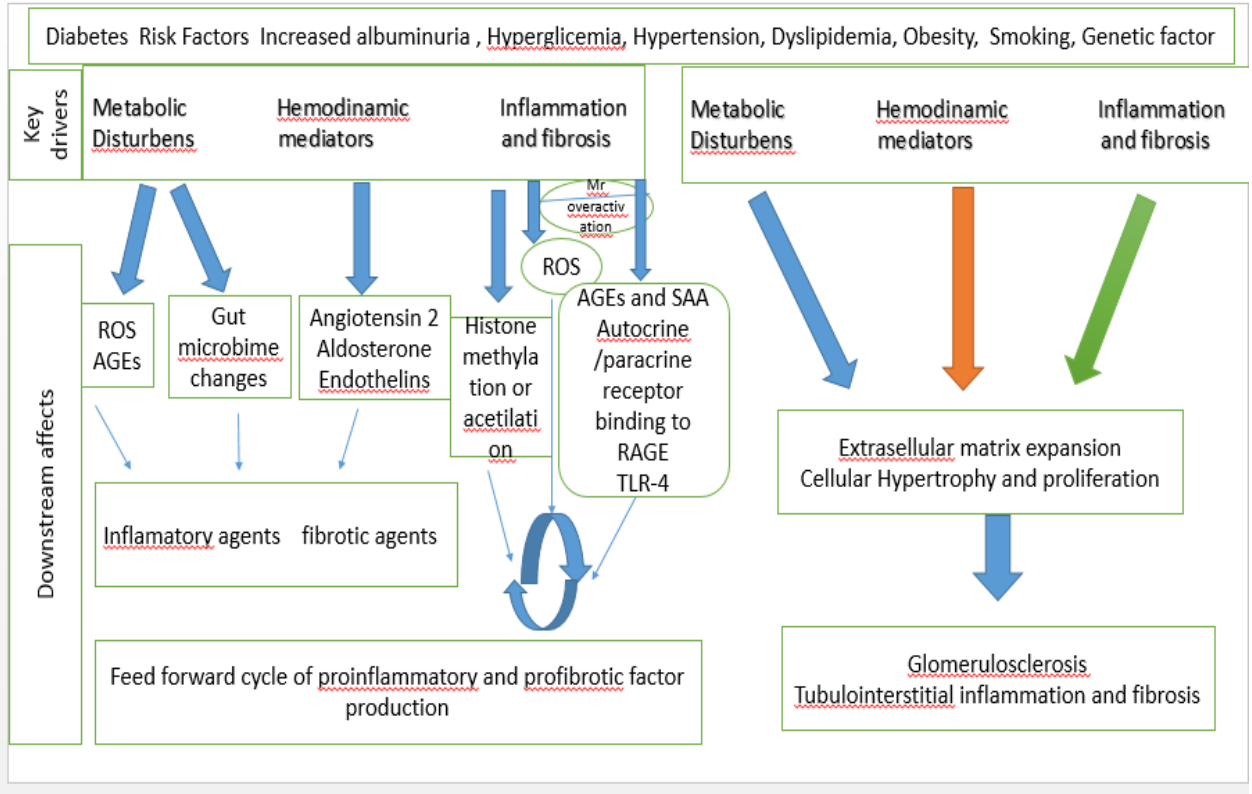

Figure 1. The diagram shows the correlation of mechanical drivers in early and advanced stages of kidney damage in diabetes. Kidney damage in diabetes is sudden and progressive. AGE, advanced glycation end product; CKD, chronic kidney disease; CTGF, connective tissue growth factor; DKD, diabetic kidney disease; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MMP-9, matrix metalloproteinase 9; MR, mineralocorticoid receptor; PAI-1, plasminogen activator inhibitor; RAGE, receptor for advanced glycation end product; ROS, reactive oxygen species; SAA, serum amyloid A; TGF-β, transforming growth factor beta; TLR-4, toll-like receptor-4; TNF-α, tumor necrosis factor alpha.

Notably, the newer glucose-lowering agents, SGLT2 inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), can prevent CKD progression in T2D, independent of their glycemic effects. By ameliorating glucotoxicity through decreasing glucose influx into proximal tubular cells, SGLT2 inhibitors induce potent anti-inflammatory effects. In preclinical models of diabetes, SGLT2 inhibition suppresses hyperglycemia-induced reactive oxygen species generation and AGE formation within proximal tubular cells and attenuates surrounding tubulointerstitial inflammation and fibrosis. GLP-1 RAs also downregulate proinflammatory pathways in nonpancreatic organs. In rodent models of diabetes, treatment with a GLP-1 RA decreased oxidative stress, transforming growth factor-beta 1 (TGF-β1), intercellular adhesion molecule-1, tumor necrosis factor-α, IL-1β, and proinflammatory macrophages in the kidney. GLP-1 RAs may prevent oxidative stress by inhibition of nicotinamide adenine dinucleotide phosphatase oxidase through cyclic adenosine monophosphate–dependent protein kinase A activation and upregulation of heme oxygenase-1. Inhibition of nuclear factor κB signaling by GLP-1 RAs is another proposed mechanism for the suppression of proinflammatory cytokine and chemokine expression.

Dietary and gut microbiome alterations

AGEs exposure can occur through the diet as well as via hyperglycemia. Dietary AGEs that escape gastrointestinal absorption interact with colonic microbiota, triggering local inflammation and release of inflammatory mediators. Activation of RAGE-dependent signaling in the gut causes mucosal barrier dysfunction and translocation of microbial proinflammatory mediators into the systemic circulation. As CKD progresses, greater amounts of ammonia and urea cause a shift toward Gram-negative bacteria in the gut. Lipopolysaccharides from their cell walls bind toll-like receptor-4 to increase local cytokine production, recruitment of inflammatory cells, and the release

of lipopolysaccharides. Exposure of toll-like receptor-4 on podocytes, and perhaps other kidney cells, to these lipopolysaccharides may lead to injury, inflammation, and fibrosis. Diabetes-associated reduction in protective short-chain fatty acids from the microbiota also promotes gut inflammation and epithelial cell disruption.

Genetic predisposition and epigenetic modifications

Complex chronic conditions, especially those that are essentially "diseases within diseases," such as the development of kidney disease in diabetes, present major challenges for deciphering reproducible genetic contributions to susceptibility and severity. Advances in acquiring large datasets in diabetes and genome-wide association studies have yielded new insights that shed light on predisposition to DKD. Missense mutations in the *COL4A3* gene, which encodes a major structural component of the glomerular basement membrane (GBM), have long been known to cause Alport syndrome.[48] Recently, another variant in *COL4A3* (rs55703767) has been linked to protection from albuminuria or "diabetic nephropathy" in patients with T1D, suggesting that this variant may prevent disordered collagen expression. Notably, protection from DKD with this *COL4A3* variant was most evident in individuals with T1D and high levels of glycated hemoglobin. This *COL4A3* variant is also associated with less GBM thickening and glomerulosclerosis among patients with either T1D or T2D who had kidney biopsy and genetic data. Thus, a "second-hit" phenomenon may be operative such that the variant reduces consequences of hyperglycemia, leading to kidney damage. Variants in other genes related to collagen pathophysiology and kidney fibrosis (*DDR1*, *COLEC11*, BMP7) are also associated with various DKD phenotypes.

In contrast to protective genetic variants, *APOL-l G1/G2* alleles observed in people of African ancestry promote development and progression of nondiabetic CKD, often when accompanied by a "second hit," for example, viral illness accompanied by a high interferon state. Another *APOL-1* variant (rs9622363) has been recently reported to be associated with kidney failure in a large genome-wide association study meta-analysis of African American people with T2D, suggesting that it may increase the risk of DKD progression. Among a European cohort with T2D, a *GABRR1* gene variant (rs9942471) was highly associated with microalbuminuria.

This gene is upregulated in glomerular diseases characterized by inflammation and fibrosis. In addition, to genetic architecture *per se*, epigenetic changes such as DNA methylation influence the genotype effect on DKD. A comprehensive analysis integrating genetics and epigenetics from a cohort of people with DKD noted distinct cytosine methylation changes that regulate immune function and inflammation including clearance of apoptotic cells by macrophages and complement activation. Genetic studies have been challenged by limited availability of large datasets for individuals with genotyping and various presentations of DKD. Linking genetic attributes to DKD is a key piece of the puzzle that will be central to further unraveling disease susceptibility and potential therapeutic targets.

Intensively controlling hyperglycemia only modestly reduces the risk of DKD onset or progression in people with long-term diabetes.

Past hyperglycemia leads to long-lasting epigenetic modifications, for example, histone methylation or acetylation, and subsequent upregulation of proinflammatory and profibrotic genes. Consequently, pathways initially activated by metabolic disturbances may become self-perpetuating.[33]

Diagnosis

1. Clinical features of DN

The hallmark of established DN is persistent albuminuria (category A3, severely increased), with co-existing retinopathy and no evidence of alternative kidney disease. In T1DM, this definition is highly specific, that is, if these features are present then the histological picture will almost certainly be that of diabetic glomerulopathy. It is rare for DN to manifest in people with T1DM in the first 10 years following diagnosis, but between 10 and 20 years the incidence of DN is approximately 3% per year. Overall, approximately 15% of people with T1DM have severe (A3) albuminuria and a further 15%

display moderate (A2) albuminuria. After 20 years, the incidence rate declines so that people with normal renal function and normal urinary albumin excretion after 30 years of T1DM are at lower risk of developing DN.8 Therefore, the risk of developing DN varies between individuals and is dependent not only on duration of T1DM, but it is also influenced by other factors, such as glycaemic control, blood pressure and genetic susceptibility.

2. Histological features of DN

Kidney biopsy is used to make the diagnosis in only a minority of cases of DN, but the typical histological features are described in an international classification system. Classes I to IV are characterized by thickening of the glomerular basement membrane, mesangial expansion, nodular sclerosis (Kimmelstiel-Wilson lesion) and severe glomerulosclerosis, respectively. In addition to these characteristic glomerular features, interstitial fibrosis and tubular atrophy (IFTA), interstitial fibrosis, arteriolar hyalinosis and arteriosclerosis are frequently also present. The pathophysiology of DKD is discussed further elsewhere in this issue of Diabetes, Obesity and Metabolism.

3. Moderately increased albuminuria (A2)

As well as indicating increased cardiovascular risk in both T1DM and T2DM, the traditional paradigm is that the onset of moderately increased albuminuria (A2), previously termed microalbuminuria, predicts the onset of established DN.

4. Methodological aspects of assessing albuminuria

In addition to varying clinical trajectories, the assessment of albuminuria is made more complex due to marked intra-individual variation in albumin excretion. In a cohort of proteinuric CKD patients who submitted three separate urine samples, the coefficient of variation for ACR was 29.7% (in random samples) and 32.5% (in early morning samples).This variability is also seen with measurements of urine albumin excretion rate, where it is further exaggerated by the challenges of accurate collection of timed or 24-hour urine samples. This, coupled to the inconvenience of measuring albumin excretion, means that ACR is the preferred method for assessing albuminuria in clinical practice. Most guidelines, including those from the American Diabetes Association (ADA), the National Institute for Health and Care Excellence (NICE) and the European Association for the Study of Diabetes (EASD) suggest annual screening with ACR to detect moderate (A2) albuminuria in all people with diabetes, with a requirement for repeat testing to confirm elevated results.It is also important to consider this biological variation in ACR values when monitoring serial changes or response to treatment, and caution should be taken when interpreting change between two measures; examining serial trends is a more reliable approach. Finally, clinicians should be aware of conditions that may result in transient increases in albuminuria and risk erroneous diagnosis. These include urinary tract infection; active systemic infection/inflammation; heavy exercise in the preceding 12 to 24 hours; heart failure; severe hypertension; menstruation; and severe hyperglycaemia. In addition, urinary ACR results can be difficult to interpret in the setting of long-term urinary catheters and in those with an ileal conduit. Urine dipstick testing is not useful for quantifying albuminuria and is not recommended for monitoring the degree of albuminuria over time.

5. Non-albuminuric DKD

It is increasingly recognized that reductions in eGFR can occur in the setting of normal urinary albumin excretion in both T1DM and T2DM. In general, non-proteinuric CKD often points towards aetiologies that are ischaemic in nature or in which tubulo-interstitial pathologies predominate. However, non-proteinuric DN has also been described in association with the typical histopathological changes of diabetic glomerulopathy.

6. Clinical approach to diagnosis of DKD

In many cases, DKD is a clinical diagnosis. A kidney biopsy is the gold standard test for diagnostic and prognostic information, but in most centres is usually only performed when an alternative renal pathology is suspected.

Screening

DKD usually does not cause symptoms, so guidelines from the ADA and KDIGO group recommend that all people with diabetes should have renal function and albuminuria measured at diagnosis and annually thereafter in T2DM; in T1DM, this can start from 5 years after diagnosis. Albuminuria is best assessed using ACR measurements on spot urine samples (ideally early morning samples); timed or 24-hour urine collections to measure albumin excretion are also appropriate although less convenient and more prone to collection errors. Renal function should be assessed using a serum-creatinine based eGFR calculation (CKD-EPI equation recommended due to its superior performance in the eGFR range 60-90 mL/min/1.73 m^2).

Confirmation of persistent abnormalities

If a reduction in eGFR or an increase in albuminuria is detected, this should be confirmed on repeat testing over 3 to 6 months; a minimum of two elevated ACR levels more than 3 months apart are required before an individual is considered to have increased albuminuria. This is to differentiate from transient changes as well as to account for the intra-individual variation that is seen in ACR. Similarly, two eGFR values below 60 mL/min/1.73 m^2 at least 90 days apart are required to make a diagnosis of CKD.

Clinical diagnosis of DKD

In T1DM, a clinical diagnosis of DKD can be made when there is persistent moderate (A2) or severe (A3) albuminuria or a persistent reduction in eGFR to <60 mL/min/1.73 m^2, occurring at least 5 years after onset of diabetes. In over 95% of cases, diabetic retinopathy will also be present,7 and there should be no clinical suggestions of alternative kidney disease (see later). Albuminuria is not required to make a diagnosis of DKD in the setting of a persistently reduced eGFR, but this clinical scenario should prompt consideration of other forms of non-albuminuric kidney disease (see later), as should albuminuria in the absence of retinopathy.

In T2DM, the clinical diagnosis can be more challenging due to the increased heterogeneity of clinical presentation, although the same principles of persistent albuminuria or persistently reduced eGFR apply. Again, albuminuria does not have to be present to make a diagnosis of DKD providing eGFR is persistently <60 mL/min/1.73 m^2. Longer duration of diabetes and presence of retinopathy are important pointers towards the diagnosis when they are present, but neither a short duration of diabetes nor absence of retinopathy are useful to rule out DKD in T2DM. It is therefore important to evaluate for features that may indicate alternative forms of kidney disease and proceed to renal biopsy when there is diagnostic uncertainty.

Non-diabetic forms of kidney disease may be suggested by the following:

Atypical trajectory of eGFR decline or onset of albuminuria. Rapid declines in eGFR (>5 mL/min/year) or sudden onset of albuminuria are not typical of DN, nor is severe albuminuria in the first 5 years of T1DM. Looking at serial eGFR trends will help to identify previous episodes of AKI, which are increasingly recognized to be associated with CKD onset and progression.

Very severe albuminuria (ACR > 300 mg/mmol or > 3000 mg/g) or nephrotic syndrome. Although DN is a well-recognized cause of nephrotic syndrome, primary glomerular disease is more likely in this setting, particularly when the nephrotic syndrome has an acute onset.

Active urinary sediment. Non-visible haematuria is not a classical finding in DN but can occur. The presence of haematuria on urinalysis is not particularly helpful and has poor ability to discriminate between diabetic and non-diabetic kidney disease with a c-statistic of only 0.59 (0.54-0.63). However, the presence of red cell casts or dysmorphic red cells on urine microscopy is much more likely to signify an alternative pathology, typically a glomerulonephritis.

Diagnosis of or clinical features that are suspicious for another systemic disease that commonly causes kidney disease (e.g., connective tissue disorders, HIV).

Family history of non-diabetic forms of kidney disease.

Differential diagnoses to consider in the setting of non-albuminuric DKD

Although non-albuminuric DN is well described, this presentation should prompt evaluation for the following:

Ischaemic nephropathy. Suggested by vascular disease elsewhere, smoking history, hypertension, aortic disease or asymmetric kidneys on renal ultrasound. Sometimes, this scenario is incorporated under the umbrella term of DKD (ie, without renal biopsy), and several of the risk factors for ischaemic nephropathy are very common in people with diabetes. Renovascular disease can also be suggested by large (>30%) declines in eGFR after initiation of RAAS inhibitors.

Dysproteinaemia-related renal disease. There are a variety of renal diseases associated with dysproteinaemias that are initially screened for with serum electrophoresis and assay of serum free light chains. This includes monoglonal gammopathy of renal significance, defined as a clonal proliferative disorder that produces a nephrotoxic monoclonal immunoglobulin, but does not meet the treatment criteria for a specific haematological malignancy.

Previous episodes of AKI.

Tubulointerstitial nephritis (TIN), classically associated with eosinophilia and urinary leukocytes but can present with normal urinary sediment. TIN is often due to medications (eg, non-steroidal anti-inflammatory drugs, proton-pump inhibitors, antibiotics, diuretics), and a careful medication history to establish temporal links between initiation of culprit medications and onset of eGFR decline can be useful. Diagnosis requires kidney biopsy.[34]

Diabetes management in chronic kidney disease.[35]

1. Comprehensive care

Patients with diabetes and CKD have multi-system disease that requires treatment including a foundation of lifestyle intervention (healthy diet, exercise, no smoking) and pharmacologic risk factor management (glucose, lipids, blood pressure).

2. Nutrition intake

Patients should consume a balanced, healthy diet that is high in vegetables, fruits, whole grains, fibre, legumes, plant-based proteins, unsaturated fats, and nuts; and lower in processed meats, refined carbohydrates, and sweetened beverages. Sodium (<2 g/day) and protein intake (0.8 g/kg/day) in accordance with recommendations for the general population should be followed.

3. Glycaemic monitoring

It is advised to monitor glycaemic control with haemoglobin A1c (HbA1c) in patients with diabetes and CKD. For patients with advanced CKD (particularly those on dialysis), reliability of HbA1c decreases and results should be interpreted with caution. Continuous glucose monitoring (CGM) or self-monitoring of blood glucose (SMBG) may also be useful, especially for treatment associated with risk of hypoglycaemia.

4. Glycaemic targets

Targets for glycaemic control should be individualised, ranging from <6.5% to <8.0%, taking into consideration risk factors for hypoglycaemia, including advanced CKD and type of glucose-lowering therapy.

5. Sodium/glucose cotransporter-2 inhibitors (SGLT2i)

SGLT2i should be initiated for patients with type 2 diabetes (T2D) and CKD when estimated glomerular filtration rate (eGFR) is ≥30 ml/min/1.73 m2 and can be continued after initiation at lower levels of eGFR. SGLT2i markedly reduce risks of CKD progression, heart failure, and atherosclerotic cardiovascular diseases, even when blood glucose is already controlled.

6. Metformin

Metformin should be used for patients with T2D and CKD when eGFR is ≥30 ml/min/1.73 m2. For such patients, metformin is a safe, effective, and inexpensive drug to control blood glucose and reduce diabetes complications.

7. Glucagon-like peptide-1 receptor agonists (GLP-1 RA)

In patients with T2D and CKD who have not achieved individualised glycaemic targets despite use of metformin and SGLT2i, or who are unable to use those medications, a long-acting GLP-1 RA is recommended as part of the treatment.

8. Renin-angiotensin system (RAS) blockade

Patients with type 1 diabetes (T1D) or T2D, hypertension, and albuminuria (persistent albumin-to-creatinine [ACR] >30 mg/g) should be treated with a RAS inhibitor (angiotensin-converting enzyme inhibitors [ACEi] or angiotensin II receptor blockers [ARB]), titrated to the maximum approved or highest tolerated dose. Serum potassium and creatinine should be monitored.

9. Approaches to management

A team-based and integrated approach to manage these patients should focus on regular assessment, control of multiple risk factors, and structured education in self-management to protect kidney function and reduce risk of complications.

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