Endotext

DIABETIC KIDNEY DISEASE

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ABSTRACT

Diabetes is the most common cause of end-stage kidney disease (ESKD) in the US and other developed countries. Diabetic nephropathy is a chronic condition characterized by a gradual increase in urinary albumin excretion, blood pressure levels and cardiovascular risk, and declining glomerular filtration rate (GFR), which can progress to ESKD. Chronic kidney disease (CKD) is common among patients with diabetes, and it develops in approximately 50% of the patients with type 1 diabetes (T1D) and 30% of those with type 2 diabetes (T2D). Patients with diabetes should be screened for CKD annually. Screening should include both albuminuria measurements and estimates of GFR. The kidney structural changes of diabetic nephropathy are unique to this disease, and closely correlate with kidney function. Multiple factors are associated with CKD in diabetes, and patients with diabetes often require multiple therapies aimed at prevention of progressive CKD and its associated co-morbidities and mortality. Management of cardiorenal risk factors, including lifestyle modifications (diet, exercise, and stop smoking), glucose, blood pressure and lipid control, use of agents blocking the renin angiotensin aldosterone system and use of SGLT2 inhibitors in patients with T2D and other agents with proven renal or cardiovascular benefit are the cornerstones of therapy.

INTRODUCTION AND EPIDEMIOLOGY

Diabetes and its complications are a substantial public health problem. In 2021, 10% of the global population (about 537 million adults) were living with diabetes (1). It is estimated that by 2045 this will rise to 784 million (1). Moreover, in a large proportion of patients, diabetes is undiagnosed. The estimates for the increased number of adults with diabetes vary largely according to the geographic region, going from a predicted 13% increase in Europe to a predicted 129% increase in Africa in the next 25 years (1), including a 24% increase in North America and Caribbean. It is estimated that over one in ten (37.3 million) Americans have diabetes, and one in three adult Americans (96 million Americans) have prediabetes (https://www.cdc.gov/diabetes/library/features/diabetes-stat-report.html).

While in populations of European origin, nearly all children and adolescents have type 1 diabetes (T1D),

in certain populations (e.g., Japan), type 2 diabetes (T2D) is more common than T1D in this age group. Although the incidence of T1D is also increasing around the globe (2, 3), the rapid increase in the incidence of T2D among children and adolescents is alarming, and it has been linked to increased obesity rates and physical inactivity in this group.

Diabetes is associated with increased mortality and morbidity, and it is the main cause of incident end-stage kidney disease (ESKD) in the US and other developed countries (4). In the US alone, diabetes is responsible for more than 47% of the new ESKD cases. This is in large part due to T2D as most patients with diabetes have T2D rather than T1D. However, the proportion of individuals starting kidney replacement therapy due to diabetes varies significantly, ranging from 13% in China to 66% in Singapore (4). The likelihood of a patient with diabetes developing chronic kidney disease (CKD) is about 40% for patients with T1D and 30% for those with T2D, while the likelihood of a patient with diabetes developing ESKD is lower than that, as a large proportion of these die prematurely, especially from cardiovascular causes, before progressing to ESKD. ESKD is devastating to the individual and of enormous financial and social consequences.

PATHOPHYSIOLOGY

Diabetic nephropathy is a chronic condition that develops over many years. It is characterized by a gradual increase in urinary albumin excretion, blood pressure levels, and cardiovascular risk, declining glomerular filtration rate (GFR) and eventual ESKD. Diabetic nephropathy is associated with characteristic histopathological features (5, 6). About 25 to 50% of individuals with T1D (7, 8) and 45-57% of those with T2D (9-12) have progressively declining GFR with no or minimal albuminuria. Non-albuminuric renal impairment was the predominant phenotype among youth with T1D (13) and also among patients with T2D (14) in Italy, and a strong predictor of mortality (15). T1D patients with non-albuminuric CKD were older (8, 16) at evaluation and at T1D onset (16), were more often female (8, 16), had lower HbA1c (8, 16), total cholesterol, LDL-cholesterol, triglyceride levels (8), and serum uric acid levels (8, 16), had higher estimated GFR (eGFR) (8), were less often hypertensive (8, 16) and less likely to have retinopathy (8, 16) or to smoke (8, 16) than patients with albuminuric CKD (14, 15, 17, 18). HbA1c and blood pressure levels were higher and HDL-cholesterol was lower among non-albuminuric youth with type 1 diabetes and CKD as compared to patients with normal renal function (13). T2D patients with non-albuminuric CKD were also older (19), more often female (10, 11, 19), non-smokers (10, 11), Caucasian or Asian (10), had shorter diabetes duration (11), lower HbA1c (11), total cholesterol (12), LDL-cholesterol (12), triglyceride (11, 12), and systolic blood pressure levels (11, 12), higher eGFR (12, 19), and less often had retinopathy (11, 12) or a history of cardiovascular disease (11) than T2D patients with albuminuric CKD.

CKD in people with diabetes can be the result of diabetic nephropathy, other associated conditions such as hypertensive renal disease and obesity-related glomerulopathy, or other renal diseases, such as IgA nephropathy, focal segmental glomerulosclerosis, acute tubular necrosis, membranous nephropathy, among others (13-15). The frequency of other renal diseases depends, among others, on the prevalence of these conditions in the background population (see Excluding Other Causes of Kidney Disease below).

SCREENING, DIAGNOSIS, STAGES, AND MONITORING

Diabetic kidney disease, or CKD in diabetes, is diagnosed by measurements of kidney function. CKD

diagnosis and staging in diabetes follows the same criteria as for patients without diabetes. In the clinical setting, CKD is classically diagnosed by estimates of GFR and measurements of urinary albumin. A decreased GFR indicates loss of filtration capacity, while an elevated albuminuria indicates that an abnormal (elevated) proportion of the albumin filtered by the kidneys is being eliminated in the urine, indicating changes in barrier selectivity.

Screening

Multiple guidelines recommend annual CKD screening of patients with diabetes, starting about 5 years after diagnosis in patients with T1D and at diagnosis in patients with T2D (20-22). Screening tests should include both albuminuria measurements and estimates of GFR.

ALBUMINURIA

Albuminuria screening should be undertaken when the person is free from acute illness and in reasonably stable glucose control, as acute illnesses and acute hyperglycemia can transiently increase albuminuria. Albuminuria may also increase in the upright posture and with exercise, thus measurements are best made in an early-morning urine sample; however, a spot urine sample is acceptable if there is no alternative. Because of the high day-to-day variation in urinary albumin excretion, if the first sample is abnormal, further samples should be obtained, ideally within 1–3 months. At least two out of three measurements should be abnormal before a diagnosis of albuminuria is made. First-morning void urinary albumin-to-creatinine ratio (ACR) measurement is the test of choice, as it is less cumbersome than timed urine collections and has lower day-to-day variability as compared to other methods (23).

GFR

In the clinical setting, GFR is estimated using equations that include patients' age, sex, and serum creatinine. Serum creatinine should be measured annually, using an accredited assay standardized to the recommended isotope dilution mass spectrometry reference method (IDMS-traceable). Most laboratories currently calculate the eGFR using the serum creatinine CKD-EPI equation (https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr). Race is now optional on this equation, as its inclusion may or may not provide more precise estimates of GFR. The CKD-EPI equation estimates measured GFR more accurately than previous equations, particularly when GFR levels are greater than 60 mL/min/1.73 m^2 (24). The CKD-EPI equation also categorizes risk of mortality and ESKD more accurately than the previous MDRD equation in a wide range of populations, including those with diabetes (25, 26). In elderly patients and in those with obesity, it has been suggested that equations based on creatinine lack precision, particularly in situations where weight loss is significant, as muscle mass usually changes without changes in eGFR (27).

Although there are data suggesting that GFR estimations based on cystatin C measurements may be slightly more precise than those based on serum creatinine (28), there is no agreement that cystatin C-based estimates are superior to creatinine-based GFR estimates (29, 30). Moreover, cystatin-C measurements are not interchangeable among laboratories, and not routinely available in the majority of the centers. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend calculating cystatin-based eGFR in adults whose creatinine-based eGFR is 45–59 mL/min/1.73 m^2 without other markers of kidney disease (31). Although this may help identify individuals with falsely reduced

GFR, it is unclear if this approach improves the identification of individuals with progressive CKD compared with sequential measurements of creatinine-based eGFR. Recently, it was proposed the use of a CKD-Epi equation including both creatinine and cystatin C, and without race, for optimal precision when needed (32).

Diagnosis

CKD is diagnosed when two eGFR, at least 3 months apart, are <60 mL/min/1.73 m^2 and/or 2 out of 3 albuminuria measurements are abnormal (ACR ≥ 30 mg/g creatinine). Diagnosis should be made in the absence of an acute serious illness (31).

CKD Stages

The 2020 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD advocates that final screening status should indicate both the GFR and albuminuria status (Tables 1 and 2) (22). The information can then be used as a measure of risk of progression to ESKD, and this classifier is also a good indicator of cardiovascular morbidity and mortality (Figure 1).

Table 1. Glomerular Filtration Rate (GFR) Categories in Chronic Kidney Disease.

GFR category	GFR (mL/min/1.73 m^2)	Description
G1	≥90	Normal or high
G2	60–89	Mildly decreased[a]
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

[a]Relative to young adult level.

Table 2. Albuminuria Categories in Chronic Kidney Disease.

Category	AER (mg/24 h)	ACR (approximate equivalent)		Description	Previous terminology
		mg/mmol	mg/g		
A1	<30	<3	<30	Normal to mildly increased	Normal
A2	30–300	3–30	30–300	Moderately increased[a]	Microalbuminuria
A3	>300	>30	>300	Severely increased[b]	Proteinuria

[a]Relative to young adult level.

[b]Including nephrotic syndrome.

ACR, urine albumin:creatinine ratio; AER, albumin excretion rate.

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (mL/min per 1.73 m²) description and range				Persistent albuminuria categories description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	>90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Figure 1. Classification and prognosis of chronic kidney disease by estimated glomerular filtration rate and albuminuria. Source: Reprinted by permission from Macmillan Publishers Ltd: Kidney International, Levin A, Stevens PE (21), copyright 2014.

Monitoring Kidney Disease

Once urinary albumin excretion is abnormal, the ACR should be measured every 3 months and eGFR every 3–6 months, depending on the CKD stage (Figure 2)

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m^2) Description and range	G1	Normal to high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Figure 2. Risk of progression by intensity of coloring (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year). These are general parameters only based on expert opinion and must take into account underlying comorbid conditions and disease state, as well as the likelihood of impacting a change in management for any individual patient. CKD, chronic kidney disease; GFR, glomerular filtration rate. Source: Reprinted by permission from American Diabetes (252).

EXCLUDING OTHER TREATABLE CAUSES OF KIDNEY DISEASE

Excluding other causes of kidney disease is especially important among patients who do not follow the classical course of diabetic nephropathy disease progression. Diabetic nephropathy is a chronic disease, thus if acute decline in GFR is present, other causes should be sought. Other causes of kidney dysfunction should also be considered if proteinuria is present before 5 years of T1D duration, in the presence of active urinary sediment (acanthocytes, cellular casts, etc.), and if there are signs or symptoms of other systemic diseases. Retinopathy may or may not be present in patients with T2D and diabetic nephropathy. The frequency of other kidney diseases will also depend on the frequency of specific diseases (IgA nephropathy, for example) in the background (non-diabetic) population. Urinalysis, ultrasound of the kidney tract, measurement of autoantibodies and immunoglobulins, and kidney biopsy may help clarify the diagnosis. Studies evaluating the frequency of

other kidney diseases in patients with diabetes indicate that the frequency of other diseases varies depending on the policy and on the reasons for a kidney biopsy (33-35). When kidney biopsies are done for research purposes, the frequency of other kidney disease is extremely low among patients with T1D without CKD (36, 37) and in Pima Indians with T2D (38).

STRUCTURAL KIDNEY LESIONS IN DIABETES

In patients with T1D, glomerular lesions can be demonstrated after diabetes has been present for a few years, while in T2D they can be present at diagnosis, probably reflecting delayed diagnosis. The changes in kidney structure caused by diabetes are specific, creating a pattern not seen in any other kidney disease. The severity of these diabetic lesions correlates with functional abnormalities (decreased GFR and albuminuria) (5, 6, 36) and it is also related to diabetes duration, glycemic control, and genetic factors. These later relationships are not precise and are in line with the marked variability in diabetic nephropathy susceptibility among patients with diabetes (see Relationships between Kidney Structure and Function below).

Light Microscopy

Renal hypertrophy, the earliest renal structural change in T1D, is not reflected in any specific light microscopy findings. In some patients, glomerular structure may remain normal or near normal for many decades, while others develop progressive disease. Early changes often include arteriolar hyalinosis, thickening of the glomerular basement membrane (GBM), and diffuse mesangial expansion (5, 6, 36). In about 40-50% of patients developing proteinuria, areas of extreme mesangial expansion called Kimmelstiel-Wilson nodules, or nodular mesangial expansion can be observed. Although Kimmelstiel-Wilson nodules are diagnostic of diabetic nephropathy, they are not necessary for severe renal dysfunction to develop. Global glomerulosclerosis can also be observed, especially with progressive disease (Figure 3). Atubular glomeruli and glomerulotubular junction abnormalities can also be present in proteinuric patients with T1D (39, 40). Tubular atrophy and interstitial fibrosis, common to most chronic renal disorders, can be present at later stages.

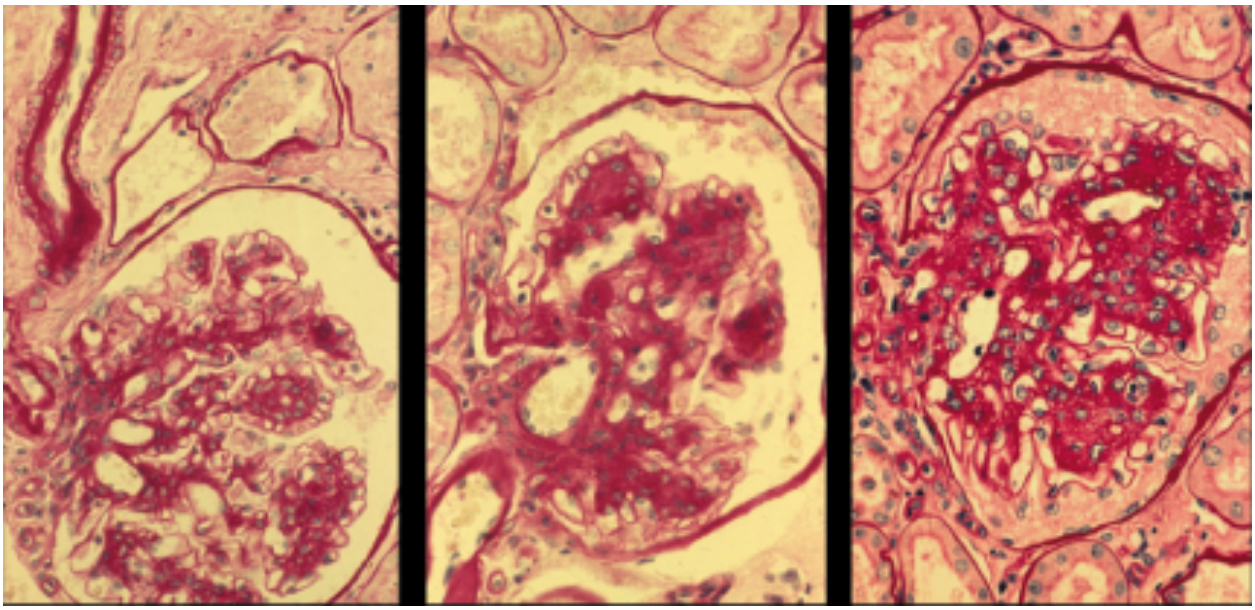

Figure 3. Light microscopy photographs of glomeruli in sequential kidney biopsies performed at baseline and after 5 and 10 years of follow-up in a long-standing normoalbuminuric type 1 diabetic patient with progressive mesangial expansion and renal function deterioration. A. Note the diffuse and nodular mesangial expansion and arteriolar hyalinosis in this glomerulus from a patient who was normotensive and normoalbuminuric at the time of this baseline biopsy, 21 years after diabetes onset [Periodic Acid Schiff (PAS) X 400]. B. 5-year follow-up biopsy showing worsening of the diffuse and nodular mesangial expansion and arteriolar hyalinosis in this now microalbuminuric patient with declining GFR (PAS X 400). C. 10-year follow-up biopsy showing more advanced diabetic glomerulopathy in this now proteinuric patient with further reduced GFR. Note also the multiple small glomerular probably efferent arterioles in the hilar region of this glomerulus (PAS X 400), and in the glomerulus in Fig. 3A above. Source: Reprinted with permission from National Kidney Foundation. Pathogenesis and Pathophysiology of Diabetic Nephropathy. Caramori ML, Mauer M. Primer on Kidney Diseases, 5th Edition, Greenberg A, et al., Copyright 2009 (253).

Immunofluorescence

Immunofluorescence findings include linear GBM and tubular basement membrane, as well as Bowman's capsule, increased staining IgG (mainly IgG4), and albumin staining. The intensity of staining is not related to the severity of the underlying lesions.

Electron Microscopy

Using morphometric techniques, the first measurable diabetic nephropathy change is thickening of the GBM, which can be detected as early as 1 and 1/2 to 2 and 1/2 years after onset of type 1 diabetes (6, 41-44) (Figure 4). Tubular basement membrane thickening can also be detected, and it parallels GBM thickening (45). Increase in the relative area of the mesangium becomes measurable by 4-5 years (6, 36, 42). Immunohistochemical studies indicate that these

changes in mesangium, GBM, and tubular basement membrane represent expansion of the intrinsic extracellular matrix components at these sites, likely including types IV and VI collagen, laminin, and fibronectin. Foot processes (podocyte) changes can be observed by electron microscopy, and the severity of these abnormalities has been associated with kidney function (46, 47). Changes in fenestrated endothelium have also been described in diabetes (47). Interstitial expansion is common to many kidney diseases. Early on in diabetes, interstitial expansion is associated with cellular alterations, while later in the disease process, when GFR is already reduced, there is increase in fibrillar collagen in the interstitium (48).

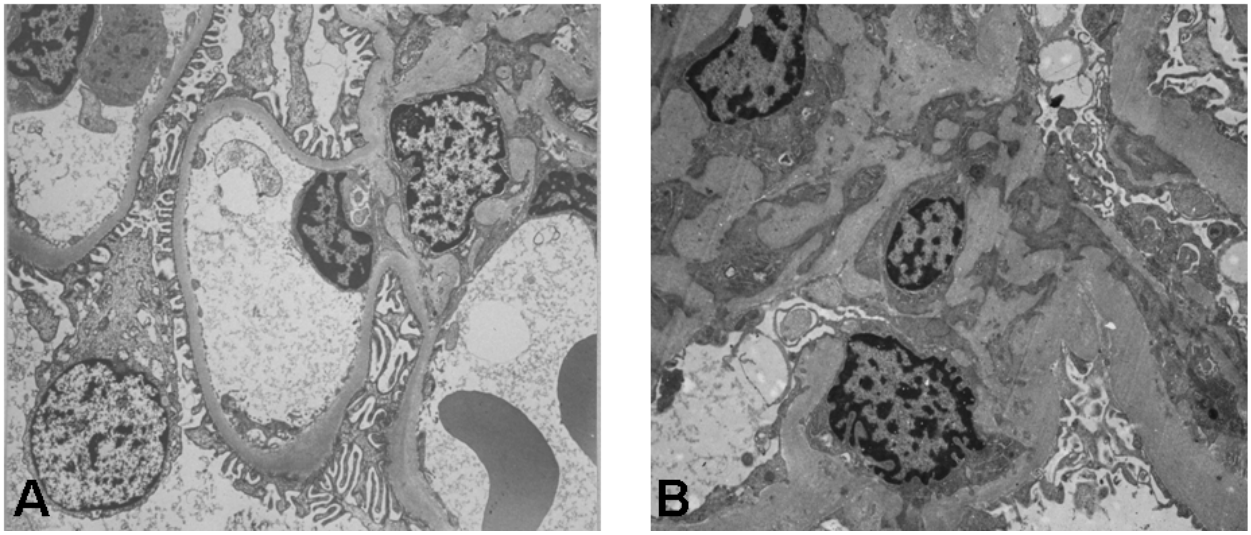

Figure 4. Electron microscopy photographs of mesangial area in normal control (A) and in type 1 diabetic patient (B) [X 3,900]. Note the increase in mesangial matrix and cell content, the glomerular basement membrane thickening and the decrease in the capillary luminal space in the diabetic patient (B). Source: Reprinted with permission from National Kidney Foundation. Pathogenesis and Pathophysiology of Diabetic Nephropathy. Caramori ML, Mauer M. Primer on Kidney Diseases, 5th Edition, Greenberg A, et al., Copyright 2009 (253).

While about 30% of patients with T2D and microalbuminuria who have had a kidney biopsy performed for research rather than clinical reasons had the classical diabetic nephropathy lesions described above, 41% have disproportionally severe interstitial fibrosis and tubular atrophy while the remaining 29% had minimal lesions with normal or near normal glomerular structure (49) (Figure 5).

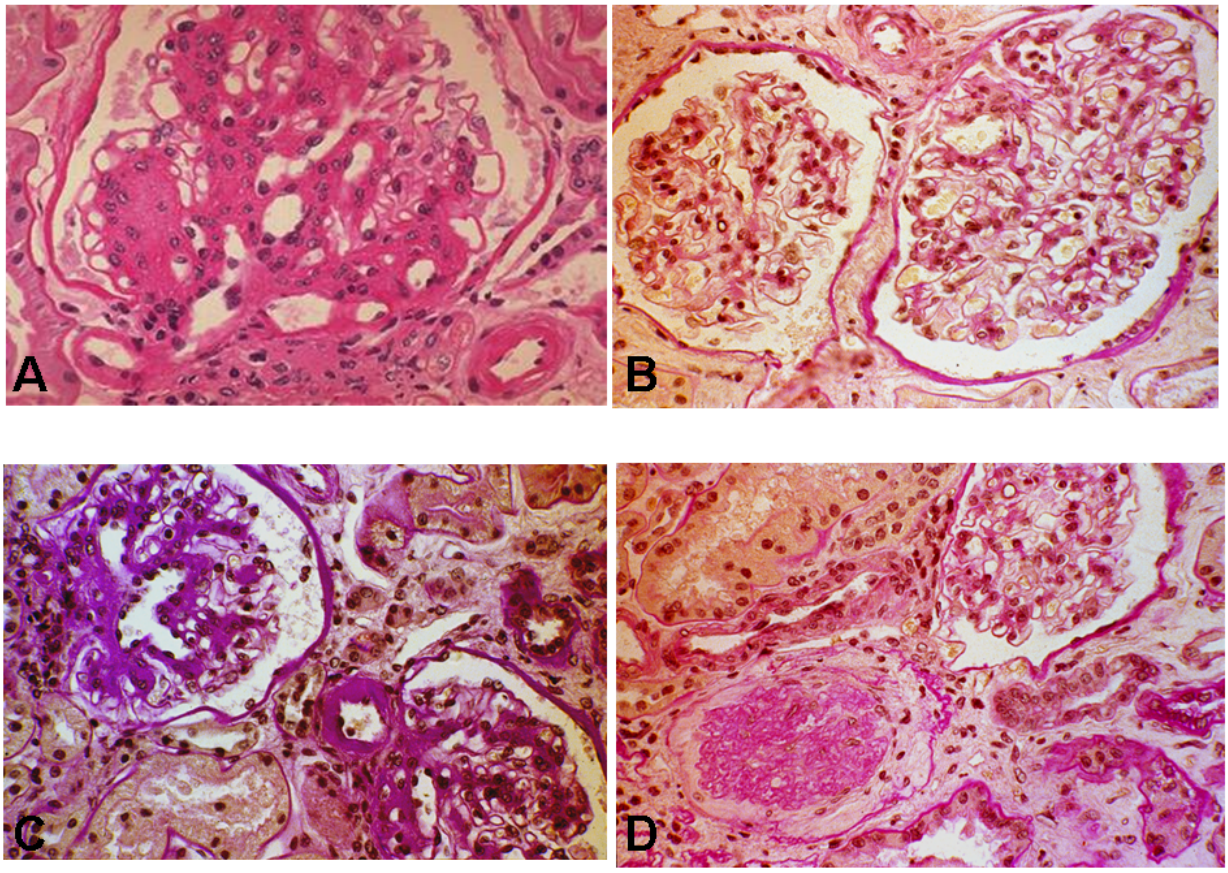

Figure 5. Light microscopy photographs of glomeruli of patients with type 1 (A) and type 2 diabetes (B-D). A. Diffuse and nodular mesangial expansion and arteriolar hyalinosis in this glomerulus from a microalbuminuric type 1 diabetic patient [Periodic Acid Schiff (PAS) X 400]. B. Normal or near normal renal structure in this glomerulus from a microalbuminuric type 2 diabetic patient (PAS X 400). This photograph was kindly provided by Dr. Paola Fioretto. C. Changes "typical" of diabetic nephropathology (glomerular, tubulo-interstitial and arteriolar changes occurring in parallel) in this renal biopsy from a microalbuminuric type 2 diabetic patient (PAS X 400). D. "Atypical" patterns of injury, with absent or only mild diabetic glomerular changes associated with disproportionately severe tubulo-interstitial changes. Note also a glomerulus undergoing glomerular sclerosis (PAS X 400). Source: Reprinted with permission from National Kidney Foundation. Pathogenesis and Pathophysiology of Diabetic Nephropathy. Caramori ML, Mauer M. Primer on Kidney Diseases, 5th Edition, Greenberg A, et al., Copyright 2009 (253).

RELATIONSHIPS BETWEEN KIDNEY STRUCTURE AND FUNCTION

In type 1 diabetes, the relationships between kidney structure and function are strong (5, 50, 51). Mesangial fractional volume and GBM width are inversely correlated with GFR, and directly correlated

with albuminuria (5, 51) and blood pressure (51, 52). Importantly, GBM width is a strong independent predictor of progression to clinically advanced kidney disease among normoalbuminuric patients with T1D (53). Among these patients, global glomerular sclerosis (53, 54) and interstitial expansion (53, 55) are present and are additional independent predictors of GFR loss (53). Although increases in podocyte foot process width also correlates with albuminuria increases in T1D (56-58), our studies in patients with T1D who had no clinical manifestations of CKD at time of their research kidney biopsies indicate that podocyte parameters did not predict long-term progression to clinical CKD (59).

RISK FACTORS

Many factors are associated with CKD in diabetes. Associations may be with both albuminuria and GFR or with one measurement only. Factors that influence the initial development of kidney disease may not be the same as factors influencing progression. Duration of diabetes is one of the strongest risk factors for diabetic nephropathy, particularly in T1D.

Glucose Control

Glucose control is an important risk factor for the development and progression of diabetic nephropathy. Data from multiple observational and intervention studies in both T1D and T2D support this view (60). There is a strong positive association between HbA1c and incident CKD (eGFR <60 mL/min/1.73 m^2), independent of other risk factors, and present even in the absence of albuminuria (61). Greater variability in HbA1c is independently associated with albuminuria and diabetic nephropathy (62-64), and variability in blood glucose levels as detected by continues glucose monitoring (CGM) has also been associated with complications (65, 66).

Blood Pressure

Blood pressure is critical in the development and progression of diabetic kidney disease. The excess prevalence of hypertension in T1D is confined to those with nephropathy (67). In young people with moderately elevated albuminuria, changes in blood pressure are subtle, perhaps manifesting only as reduced nocturnal diastolic blood pressure dipping (68). Once severely increased albuminuria is present, frank hypertension is present in 80% of patients, and is almost universal in ESKD. Variability in systolic and diastolic blood pressure independently predicts the development of albuminuria in T1D (62).

In T2D, the link between hypertension and kidney disease is less striking, perhaps due to the fact that hypertension is very common among these patients, present in 70-80% of the patients with T2D at the time of diagnosis. Almost all patients with moderately elevated albuminuria or worse have hypertension. In people with diabetic nephropathy, variability in systolic blood pressure is independently associated with the development of ESKD in patients with T1D (62) and T2D (69).

Other Metabolic Factors

Blood lipids, including triglycerides (70, 71), are associated with the development and progression of nephropathy, although the lipid phenotype alters as nephropathy progresses (72-74). Current smoking predicts the development of albuminuria (75). Insulin resistance increases the risk of albuminuria and rapid eGFR decline in patients with T1D (76) and of albuminuria in those with T2D (77). Individuals with T1D or T2D and nephropathy are more likely to have the metabolic syndrome (78, 79). Uric acid predicts the development of severely increased albuminuria

(80) and decline in GFR as well as cardiovascular events (81). Probably this association is not causal as a reduction in uric acid by treatment with allopurinol could not slow GFR decline in patients with T1D (17).

Hyperfiltration

Hyperfiltration is common at onset of T1D and it is also present in some individuals at T2D diagnosis. GFR often returns to normal as glucose is controlled, but it may remain elevated in certain individuals. Whether individuals with persistent hyperfiltration are at increased diabetic nephropathy risk remains controversial (82-85). Sodium glucose cotransporter 2 inhibitors (SGLT2i) were introduced to lower glucose in T2D and have been demonstrated to slow progression of kidney disease (see below). A marked effect on hyperfiltration in T1D with SGLT2i was suggested to reflect lowering of intraglomerular hypertension and to support lowering of hyperfiltration as an important kidney protective measure (86). On the other hand, the results in T2D were less clear (87).

Genetic Factors

Genetic factors influence susceptibility to diabetic nephropathy (85, 86). If one sibling with T1D has nephropathy, the risk for the second sibling is increased 4–8 fold compared with siblings where neither have nephropathy (88). The clustering of conventional cardiovascular risk factors and cardiovascular disease (CVD) in people with diabetic nephropathy also occurs in their parents (89, 90). This suggests that the genetic susceptibility to nephropathy also influences the associated CVD. Research kidney biopsies in siblings with T1D also demonstrated heritability in the severity and patterns of renal lesions (91). Sodium-hydrogen antiport activity (92) and mRNA expression of catalase, an antioxidant enzyme associated with diabetic nephropathy risk, (93) were also found to be, at least in part, genetically regulated in siblings concordant for T1D. It is likely multiple genes are associated with DKD, and they can be either protective or deleterious. Moreover, different loci may influence albuminuria and GFR (94). Epigenetic modifications may also be important (95).

Ethnicity

In the Unites States, the prevalence of early CKD (defined as moderately elevated albuminuria or greater and eGFR<60 mL/min/1.73 m^2) is higher in Latino and African American individuals than white people (96). A similar pattern is seen in Europe, where United Kingdom Afro-Caribbean and South Asian individuals more often have albuminuria and advanced CKD (stages 4-5) than white European individuals (97, 98). Albuminuria and CKD are also more common in Pima Indians (99) and in Māoris and Pacific Islanders (100, 101) than white Europeans. Reasons for this varying prevalence may include differing genetic influences and altered response to, or poorer access to, treatments.

Development of T2D in Youth

Individuals who develop T2D in youth have a high prevalence of hypertension and moderately elevated albuminuria (102). ESKD and death are particularly common in young people from ethnic minorities (103-105). However, in some of these populations, there is a high prevalence of non-diabetic kidney disease (106).

Albuminuria and GFR

Baseline albuminuria and eGFR independently influence the development and rate of progression of CKD (75, 107). Baseline albuminuria strongly predicts

ESKD (108). Higher levels of albuminuria in the normoalbuminuric range (109, 110) and lower eGFR (111) predict a faster decline in eGFR. Conversely a short-term reduction in albuminuria with intervention suggest reduced progression of kidney and cardiovascular complications (112, 113).

Other Risk Factors

Other risk factors for nephropathy include pre-eclampsia (114), inflammatory markers (115, 116), cytokines and growth factors (117), periodontitis (118), and serum bilirubin levels (119, 120). Obstructive sleep apnea (121) and non-alcoholic fatty liver disease are both independently associated with diabetic nephropathy (122, 123). Circulating levels of tumor necrosis factor-α receptor 1 are independently associated with the cumulative risk of ESKD in T1D and T2D (124-126).

CO-MORBIDITIES AND ASSOCIATED COMPLICATIONS

The prognosis for people with diabetes and CKD is much poorer than for those without CKD. Both albuminuria and eGFR <60 mL/min/1.73 m^2 (Figure 6 and 7) contribute independently and synergistically to the increased all-cause and cardiovascular risk (127-131).

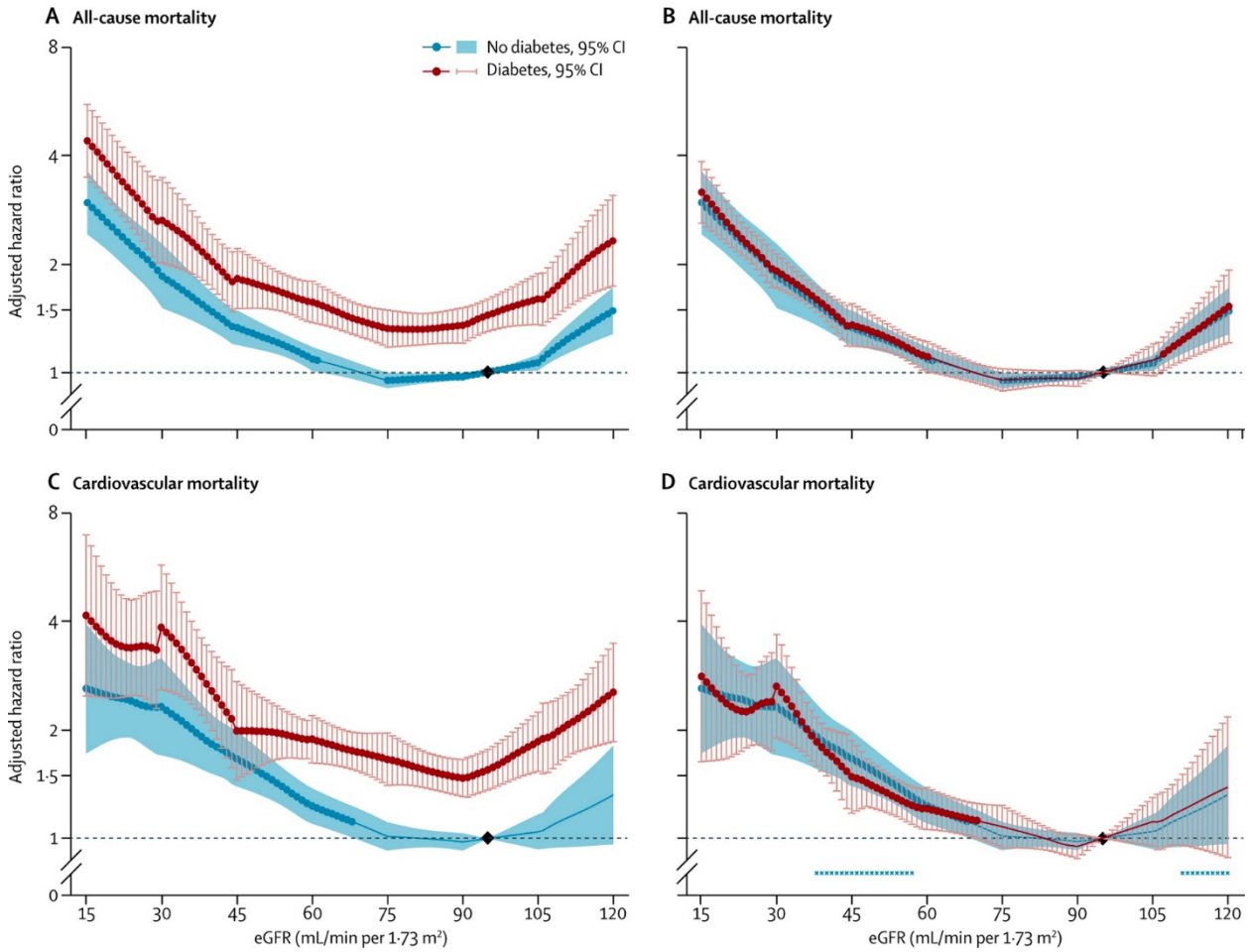

Figure 6. Declining glomerular filtration rate is associated with all-cause and cardiovascular mortality in individuals with and without diabetes. (A, B) All-cause mortality. (C, D) Cardiovascular mortality. Panels A and C use one reference point (diamond, eGFR of 95 mL/min per 1.73 m2 in the no diabetes group) for both individuals with and without diabetes to show the main effect of diabetes on risk. Panels B and D use separate references (diamonds) in the diabetes and no diabetes groups to assess interaction with diabetes specifically. Hazard ratios were adjusted for age, sex, race, smoking, history of cardiovascular disease, serum total cholesterol concentration, body-mass index, and albuminuria (log albumin-to-creatinine ratio, log protein-to-creatinine, or categorical dipstick proteinuria [negative, trace, 1+, ≥2+]). Blue and red circles denote p<0.05 as compared with the reference (diamond). Significant interaction between diabetes and eGFR is shown by x signs. eGFR=estimated glomerular filtration rate. Reproduced from Fox et al. 2012 (254), Copyright 2012, with permission from Elsevier.

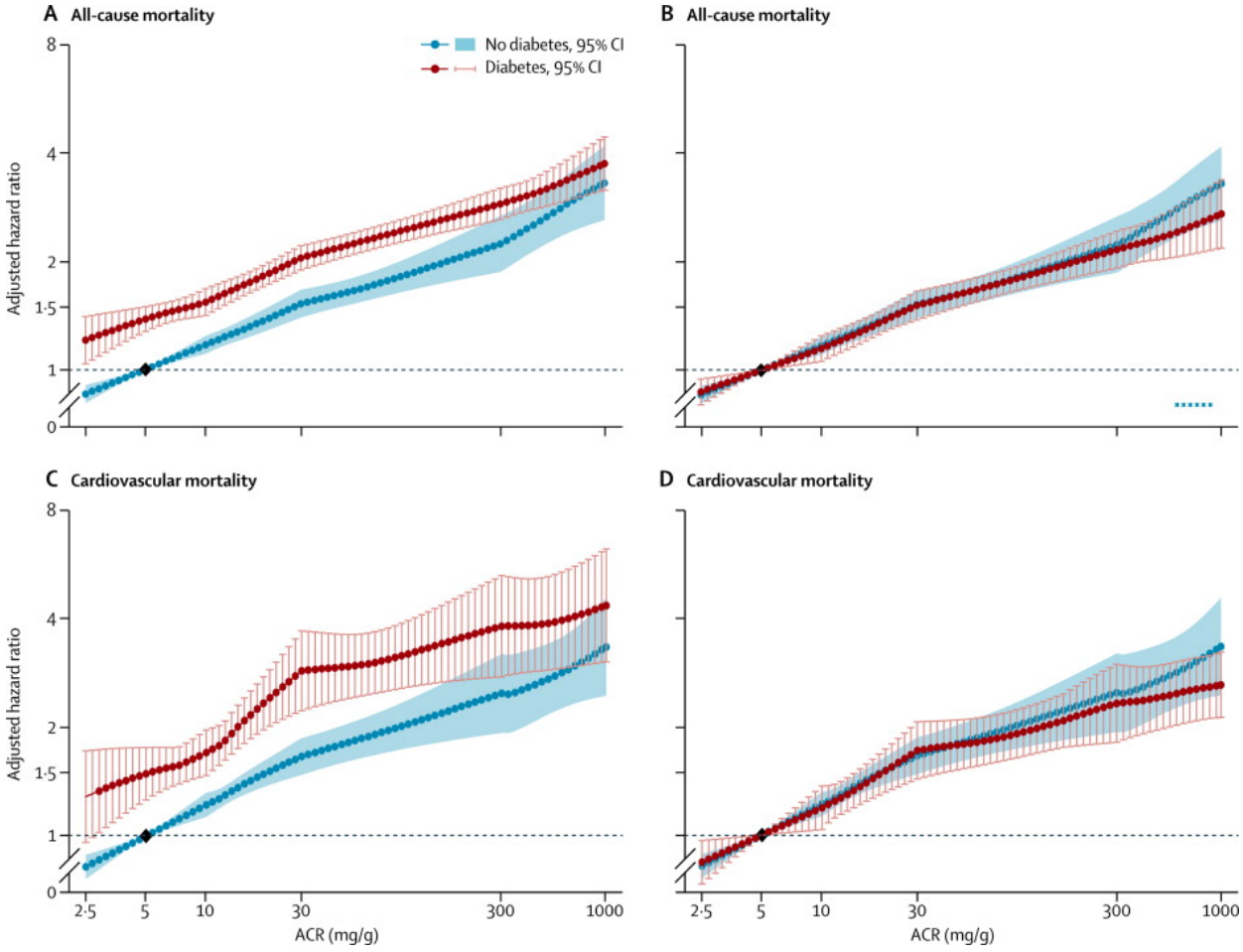

Figure 7. Increasing albuminuria is associated with all-cause and cardiovascular mortality in individuals with and without diabetes. (A, B) All-cause mortality. (C, D) Cardiovascular mortality. Panels A and C use one reference point (diamond, ACR of 5 mg/g in the no diabetes group), for both individuals with and without hypertension to show the main effect of diabetes on risk. Panels B and D use separate references (diamonds) in the diabetes and no diabetes groups to assess interaction with diabetes specifically.

Hazard ratios were adjusted for age, sex, race, smoking, history of cardiovascular disease, serum total cholesterol concentration, body-mass index, and estimated glomerular filtration rate. Blue and red circles denote p<0.05 as compared with the reference (diamond). Significant interaction between diabetes and ACR is shown by x signs. ACR=albumin-to-creatinine ratio. Reproduced from Fox et al. 2012 (254), Copyright 2012, with permission from Elsevier.

Association of Diabetic Kidney Disease with Cardiovascular Disease

TYPE 1 DIABETES

In T1D, the relative risk of premature mortality is 2–3-fold higher in moderately elevated albuminuria, 9-fold in severely increased albuminuria, and 18-fold in ESKD compared with the non-diabetic population (132). Individuals with T1D and normoalbuminuria do not have a higher risk of premature death (132, 133). CVD is 1.2-fold more common in people with moderately increased albuminuria (134) and 10-fold higher in those with severely increased albuminuria compared with those with normoalbuminuria (135). The cumulative incidence of CVD by the age of 40 years is 43% in people with T1D and severely increased albuminuria, compared with 7% in individuals with normoalbuminuria, with a 10-fold risk of coronary heart disease and stroke. In ESKD, the risk of CVD is even higher. Median survival on kidney replacement therapy is 3.84 years (136).

TYPE 2 DIABETES

In T2D, CVD risk is increased 2–4-fold with moderately increased albuminuria (137) and 9-fold in severely increased albuminuria (138). Once serum creatinine is outside the normal range, cardiovascular risk increases exponentially (139). Median survival from initiation of kidney replacement therapy is 2.16 years (136).

Microvascular Complications

Patients with diabetic nephropathy often have other microvascular complications. Significant retinopathy is almost always present in people with T1D and moderately elevated albuminuria or more. Progression of retinopathy and development of nephropathy each increases the risk for the other, supporting the notion of a common etiology (140). In people with T2D, the relationship is less strong (141). Those with classical nephropathy and progressively increasing albuminuria usually have significant retinopathy, and indeed moderately elevated albuminuria predicts the development and progression of retinopathy in T2D (142-144). In those with non-classical disease, retinopathy may be absent.

Peripheral neuropathy is also more common in diabetic nephropathy and associated with both albuminuria and declining GFR (144). Autonomic neuropathy, diagnosed by loss of nocturnal blood pressure dipping, occurs frequently (145, 146) and predicts kidney function decline (147).

PREVENTION AND TREATMENT

Although multiple strategies are now available to slow diabetic nephropathy progression, prevention of kidney disease remains crucial. The risk of developing diabetic nephropathy is particularly reduced by achievement and maintenance of good blood glucose and blood pressure control (22).

A guideline on management of diabetes in CKD from Kidney Disease Improving Global Outcomes (KDIGO) emphasize management of cardiorenal risk factors lifestyle factors (diet, exercise, and stop smoking), glucose, blood pressure, and lipids including blockade of the renin angiotensin aldosterone system and in T2D SGLT2 inhibition (Figure 8) (148).

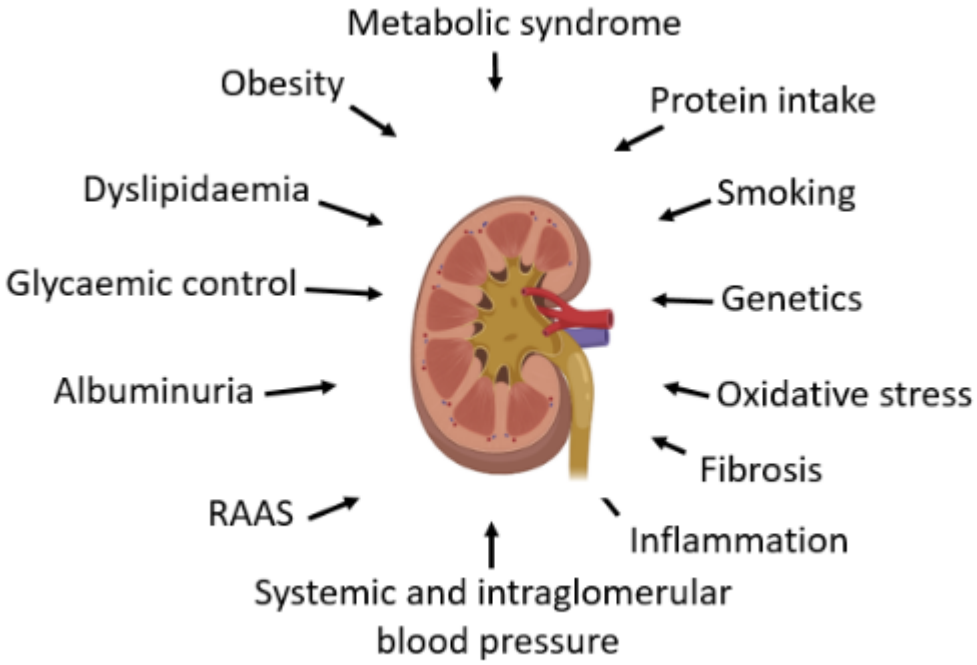

Figure 8. Putative promoters of progression of diabetic nephropathy. Source: Reproduced from Fox et al. 2012 (254), Copyright 2012, with permission from Elsevier.

Glucose Control

GLUCOSE CONTROL IN T1D

Among the participants in the DCCT who initially had normoalbuminuria, the relative risk reduction for development of moderately elevated albuminuria was 39% and for grade A3 (macroalbuminuria or proteinuria) 54% in those allocated to the intensively treated group compared with those in the conventionally managed group over the 6.5-year study (149). Mean achieved HbA1c was 7.0% and 9.1%, respectively. There is no HbA1c threshold below which risk is not reduced (150).

In the open follow-up of the DCCT cohort, the EDIC study, HbA1c in the previously intensive and conventional treatment groups became similar, ~8.0%. Despite this, the incidence of moderately and severely increased albuminuria grades (151), eGFR <60 mL/min/1.73 m^2, and ESKD (151) were significantly reduced in those who had previously received intensive management, as summarized in Table 3. These results are supported by an observational study of individuals with T1D and CKD stages 1–3 with severely increased albuminuria at baseline (152). The cumulative risk of ESKD after 15 years was significantly lower in those whose HbA1c

improved compared with those whose HbA1c remained stable or deteriorated. Hence improving glucose control significantly reduces the risk of development and progression of all stages of diabetic nephropathy in T1D. The beneficial effects extend far beyond the actual period of good glucose control, a phenomenon termed "metabolic memory." In highly selected patients undergoing serial kidney biopsies after successful pancreas transplantation, kidney structural changes regressed after 10 but not 5 years (153). Thus, prolonged periods of "normoglycemia" are necessary to reverse kidney structural changes. It has been suggested that not only mean glycemic level as reflected by HbA1c, but also time in target glycemic range is important for the development of renal complications (154). In a small, study insulin pump therapy was associated with less variability compared to multiple daily insulin injections, and the reduced variability and improved time in range contributed to decline in albuminuria in T1D with increased albuminuria, beyond change in HbA1c (65).

Table 3. Kidney Benefits of Intensive Insulin Therapy Demonstrated by the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Cohort.

Parameter	Duration of observation (years)	Conventional insulin therapy	Intensive insulin therapy
Moderately elevated albuminuria	8	15.8%	6.8%
Severely increased albuminuria	8	9.4%	1.4%
eGFR <60 mL/min/1.73 m^2	22	46 (*n*)	24 (*n*)
ESKD	22	16 (*n*)	8 (*n*)

n, Number.

eGFR estimated glomerular filtration rate; ESKD, end-stage kidney disease.

Source: Data from (142, 145).

GLUCOSE CONTROL IN T2D

In the UKPDS, although the mean achieved HbA1c in the intensively managed group was 7.0% compared with 7.9% in the less strictly managed group, there was a 30% reduction in the relative risk of developing moderately or severely increased albuminuria after 9–12 years (155). No threshold of HbA1c and risk was observed, suggesting that the lower the HbA1c, the lower is the risk of nephropathy (156). In the open follow-up of the UKPDS cohort, HbA1c was similar in the previously intensively and conventionally managed groups after 1 year (157). Despite this, microvascular risk remained lower, confirming the "metabolic memory" seen in the DCCT/EDIC study. In the ADVANCE study, the HbA1c achieved in the intensively managed group was 6.5%, compared with 7.3% in the standard care group (158). In the intensive group there was a 9% relative risk reduction in new-onset moderately elevated albuminuria, a 30% reduction in the development of severely increased albuminuria, and a 65% reduction in ESKD over 5 years (159). The ACCORD study also demonstrated significant reductions in new onset moderately and

severely increased albuminuria and of ESKD with intensive glucose management (160). Progression of albuminuria was reduced and regression increased. However, in those with CKD at baseline, the risk of all-cause and cardiovascular mortality was significantly increased in the intensive glucose management group (161). Hence the kidney benefits of extremely tight glucose control were outweighed by the excess mortality. A less intensive HbA1c target in individuals with T2D and duration >10 years seems sensible.

GLUCOSE CONTROL IN ESKD

Most (162-164) but not all (165) observational studies have demonstrated increasing all-cause and cardiovascular mortality with increasing HbA1c in people with diabetes on kidney replacement therapy. Some also showed a U-shaped relationship, with mortality increasing at low HbA1c levels (162, 164, 166). However, there have been no studies that demonstrated improved survival in patients with ESKD with improving glucose control. Among patients undergoing kidney transplant, improved allograft survival was demonstrated in patients with more strict blood glucose control (167).

Glucose Lowering Medications and Organ Protection

SGLT2 INHIBITORS

For over twenty years renin angiotensin system (RAS) blockade was the only recommended treatment for diabetic nephropathy. After many unsuccessful attempts in developing new therapies the first success has been with SGLT2 inhibitors. When initially tested for safety in cardiovascular outcome trials, empagliflozin showed not only a benefit on the primary endpoint major adverse cardiovascular events (168) but also a significant benefit on hospitalization for heart failure was also observed. In addition, a reduction in incident or worsening nephropathy occurred (HR 0.61; 95% CI, 0.53 to 0.70) (169). These findings were confirmed in cardiovascular outcome trials with canagliflozin, dapagliflozin and ertugliflozin (170). Importantly the benefits on kidney outcomes were independent of baseline eGFR from <45 ml/min/1.73m2 to >90 ml/min/1.73m2 and also independent of urinary albumin creatinine ratio <30mg/g, 30-300 or >300 mg/g (171). The first study with hard renal endpoints (end stage kidney disease, significant loss of renal function) as primary endpoint using a SGLT2 inhibitor was CREDENCE showing a major benefit on renal outcome, but also on heart failure and major adverse cardiovascular events in people with type 2 diabetes, urine albumin creatinine ratio >300 mg/g and eGFR 30-90 ml/min/1.73m^2 (172). The primary outcome was a composite of end stage kidney disease, a doubling of the serum creatinine level, or death from renal or cardiovascular causes. The study was stopped early showing a benefit of canagliflozin with a HR 0.70; (95% CI, 0.59 to 0.82). These data were confirmed and extended by the DAPA-CKD study including subjects with chronic kidney disease with or without diabetes (173). EMPA-KIDNEY included participants with CKD with and without T2D as DAPA-CKD, but in addition to participants with albuminuria, EMPA-KIDNEY also included a group of study participants with impaired eGFR (20-45 mL/min/1.73m^2) and normal albumin excretion (174). This study was recently stopped for positive findings which remain to be disclosed. Whereas SGLT2i's were introduced to treat hyperglycemia, they also provide organ protection in diabetes with eGFR <45 mL/min/1.73m^2 where there is no effect on blood glucose. Dapagliflozin and empagliflozin were also able to reduce heart failure hospitalization in people with heart failure with reduced ejection fraction (175), and empagliflozin was the first agent reported to reduce hospitalization for heart failure in people with heart failure with preserved ejection fraction, with similar benefit in those with and

without diabetes (86, 176). In the DAPA-CKD study it was also demonstrated that dapagliflozin was able to reduce progression of CKD, hospitalization for heart failure and mortality in people with CKD with type 2 diabetes, but just as well in people with non-diabetic CKD (173) (Table 4).

Table 4. Summary of SGLT2 Inhibitors on Renal Disease

	Number	Mean Follow-up (years)	Hazard Ratio* (95% CI)	P value
EMPA-REG Empagliflozin	7,020	3.1	0.54 (0.40-0.75	<0.001
CANVAS Canagliflozin	10,142	3.6	0.60 (0.47-0.77)	--
DECLARE-TIMI 58 Dapagliflozin	17,160	4.2	0.53 (0.43-0.66)	<0.001
VERTIS-CV Ertugliflozin	8,246	3.0	0.81 (0.63-1.04)	0.08
CREDENCE Canagliflozin	4,401	2.6	0.66 (0.53-0.81)	<0.01
DAPA-HF Dapagliflozin	4,774	1.5	0.71 (0.44-1.16)	0.17
EMPEROR Empagliflozin	3,730	1.3	0.52 (0.32-0.77)	0.026
DAPA-CKD Dapagliflozin	4304	2.4	0.56 (0.45-0.68)	<0.001

*Renal composite outcomes Adapted from (177)

The explanation for the renal and cardiac benefits is not clear but multiple mechanisms have been suggested and probably glucose reduction is not very important. The inhibition of SGLT2 in the proximal tubule leads to blockade of glucose and sodium reabsorption, thus increasing distal tubular sodium delivery, which via macula densa and tubulo-glomerular feedback reduces intraglomerular pressure through constriction of the afferent glomerular arterioles. This is reflected clinically in the small dip in GFR when starting SGLT2i treatment and this mechanism has been suggested as the key mechanism behind the kidney protective effects. Reduction in blood pressure, body weight, increased uric acid excretion, and change in fuel metabolites have also been suggested to contribute (169). Blocking uptake of sodium in the proximal tubule has also been suggested to reduce oxygen consumption, thereby reducing hypoxia, leading to less inflammation and fibrosis in experimental studies and acute studies in humans were able to demonstrate improved renal oxygen availability (178).

In T2D with CKD metformin is recommended as first glucose lowering agent after lifestyle intervention, as in others with T2D, and then SGLT2 inhibitors are recommended independent of HbA1c for their organ protective effect, particularly in patients with albuminuria or heart failure (179, 180)(181) (Figure 9). In Europe the SGLT inhibitors sotagliflozin and dapagliflozin were initially approved for treatment of

T1D, however the risk for normoglycemic diabetic ketoacidosis is increased compared to T2D and there are no studies of the kidney benefit in diabetic nephropathy in T1D. Currently, sotagliflozin is not marketed and the indication for dapagliflozin for treatment of T1D was stopped, and additional studies are needed to determine whether these agents can be safely used in patients with T1D to prevent CKD and cardiovascular progression.

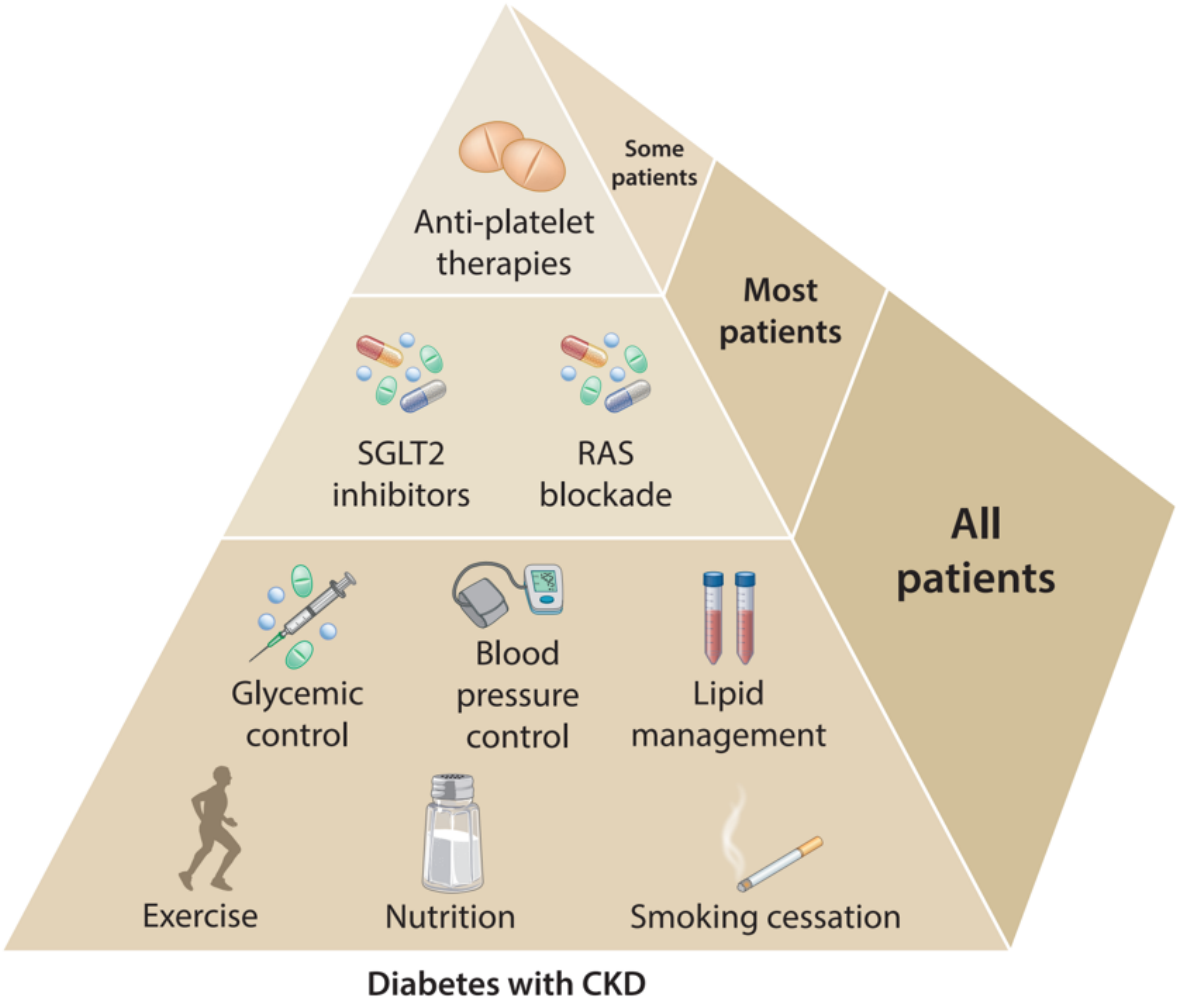

Figure 9. Patients with diabetes and CKD should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease Source: Reproduced with permission from Kidney Disease: Improving Global Outcomes (KDIGO) (172).

GLUCAGON LIKE PEPTIDE 1 RECEPTOR AGONSISTS

For some long-acting glucagon-like peptide-1 receptor agonists (GLP1-RA) (liraglutide, semaglutide, and dulaglutide) the cardiovascular outcome trials in type 2 diabetes demonstrated cardiovascular benefits, in

subjects with already existing atherosclerotic CVD (180). The benefit on CVD outcomes was also demonstrated in CKD populations and thus GLP1-RA are recommended in the treatment of T2D with diabetic nephropathy when metformin and SGLT2 inhibition cannot control glucose (Figure 10). Studies also demonstrated positive kidney effects as secondary endpoints, mostly driven by reductions in albuminuria, but also some potential effects on eGFR. A kidney benefit was supported by the AWARD 7 study with dulaglutide in T2D with CKD although the primary endpoint was glycemic control (182). Semaglutide is being tested in the FLOW study (ClinicalTrials.gov NCT03819153) to determine whether it will confer benefits on hard renal and cardiovascular outcomes among participants with T2D when compared to placebo.

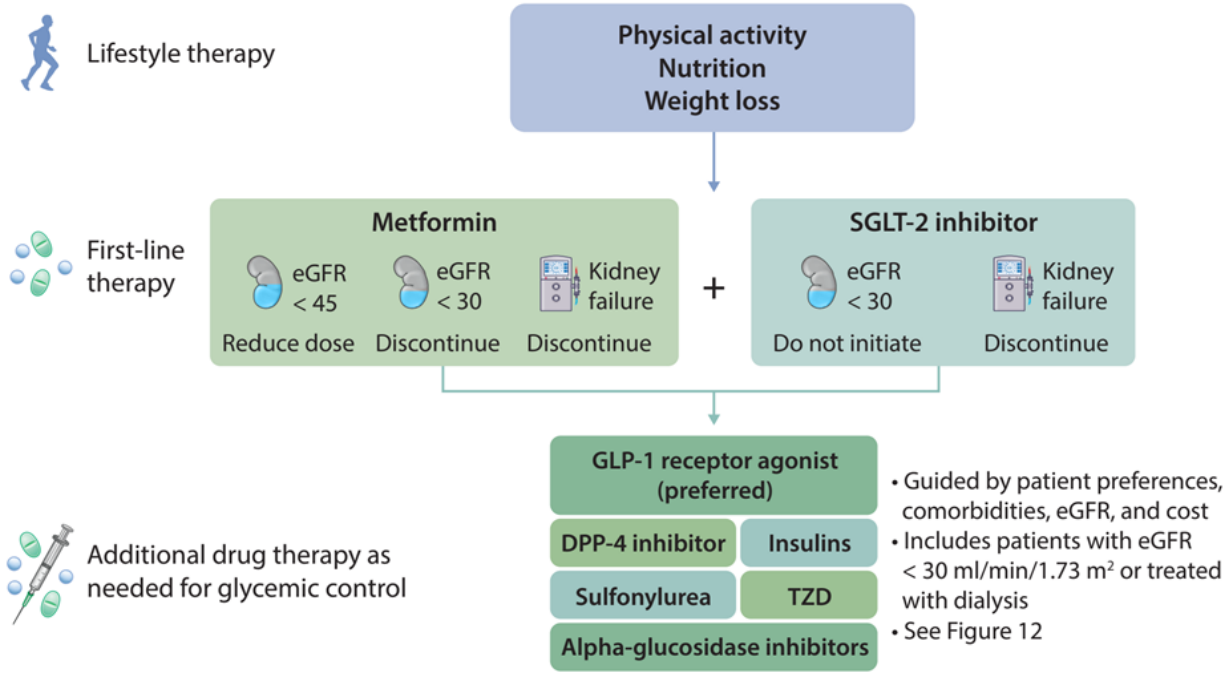

Figure 10. Antihyperglycemic Therapies in Patients with Diabetes and CKD Source KDIGO guideline on management of diabetes in CKD Source: Reproduced with permission from Kidney Disease: Improving Global Outcomes (KDIGO) (172).

Blood Pressure Control

Rigorous blood pressure control improves the prognosis in diabetic nephropathy dramatically. Conservative estimates suggest that good blood pressure management doubles the time taken from first appearance of severely increased albuminuria to need for kidney replacement therapy, from a mean of 9 to 18 years. Improved management in moderately elevated albuminuria may prevent progression and promote regression normoalbuminuria. Blood pressure and blood glucose lowering effects are independent of one another but have synergistic effects (183, 184). In contrast to glucose "metabolic memory," the benefits of blood pressure reduction are lost rapidly when control deteriorates (157).

TYPE 1 DIABETES

RAS inhibitors do not prevent moderately elevated albuminuria in normotensive people with T1D (37, 185, 186). There is also no evidence that control of hypertension in T1D and normoalbuminuria prevents progression of albuminuria and decline in kidney function. However, it seems highly likely.

Once moderately or severely increased albuminuria is present, inhibition of the RAS is the backbone of therapy, because it reduces intraglomerular pressure. A meta-analysis summarized the effects of ACE inhibitors in people with T1D and moderately elevated albuminuria (187). The odds ratio for progression to severely increased albuminuria was reduced by ACE inhibition to 0.35, and for regression to normoalbuminuria it increased to 3.07, compared with placebo treatment. After 2 years of treatment, the mean reduction in albumin excretion was 50.5% with ACE inhibition and it was greatest in those with highest baseline levels. However, the response to treatment plateaued with time, suggesting that treatment delays, rather than prevents, progression.

Addition of an ACE inhibitor to non-ACE inhibitor antihypertensive therapy reduced the risk of a doubling of the serum creatinine by 48% and the composite end-point of death, need for dialysis or kidney transplantation, by 50%, in people with T1D and with severely increased albuminuria and hypertension (188). Both benefits were independent of blood pressure. In short-term studies, the effects of angiotensin receptor blockers (ARBs) on blood pressure and urinary albumin excretion were similar to those of ACE inhibitors in T1D and severely increased albuminuria (189).

For a similar reduction in blood pressure, there is a greater reduction in protein excretion using ACE inhibitors compared with other classes of antihypertensive agents (190). This may be beneficial, as the passage of protein across the glomerular filtration barrier may accelerate the progression of nephropathy (191). Animal data show that this is due to preferential reduction in intraglomerular pressure with ACE inhibitors due to a dilatation of the efferent vessels (192). An effect on the filtration barrier has also been suggested (193).

RAS inhibitors should be offered to all individuals with T1D and albuminuria, regardless of blood pressure. The dose should be titrated up to the maximum recommended or tolerated, to obtain maximal antiproteinuric effect. If blood pressure remains >125/75 mmHg on maximum dose of RAS inhibitor, antihypertensive therapy should be intensified. Lower blood pressure reduces the rate of decline of GFR from 10–12 mL/min/year untreated to <5 mL/min/year (194). Regression from severely to moderately increased albuminuria can be achieved, with the fall in GFR reduced to <1 mL/min/year (71). The choice of agent should be made on an individual basis, as there is no evidence in T1D that any one add-on agent is better than any other. Often multiple agents are needed in CKD stage 3 and beyond.

TYPE 2 DIABETES

Control of hypertension reduces the risk of developing moderately or severely increased albuminuria (195-198). There may be a particular benefit of RAS inhibition in prevention of nephropathy (199-201) but lowering blood pressure sufficiently is the key. Achieved blood pressure in these studies was generally ~140/80 mmHg, but most guidelines now suggest a blood pressure target of 130/80 mmHg in T2D (20, 21).

As with T1D, there is good evidence in T2D that inhibition of the RAS should be the backbone of therapy if albuminuria is elevated. RAS blockade reduces progression of moderately elevated albuminuria to severely increased albuminuria (196, 202) and increases regression to normoalbuminuria (202). The benefits are at least partly independent of blood pressure lowering. In more advanced diabetic nephropathy, RAS inhibition with ARB reduces progression, defined as doubling of serum creatinine, ESKD, or death (203, 204). Hence people with T2D and moderately or severely increased albuminuria should be prescribed a RAS inhibitor, titrated to the maximum tolerated dose (205). Hyperkalemia is common in individuals with T2D and nephropathy taking an ARB and is associated with increased risk of kidney failure (206). General steps to lower potassium such as dietary advice, diuretics, discontinuation of other medications or dietary supplements which might be increasing potassium levels, or potassium binders should be considered before stopping RAS blockade (179). Introduction of a RAS inhibitor often leads to an acute decline in GFR, which then stabilizes. Individuals with the greatest initial fall in GFR have the slowest subsequent decline in kidney function (207).

Most people with T2D and albuminuria will require additional antihypertensive therapy. The choice of additional agents should be made on an individual basis, with diuretics and calcium channel blockers often being appropriate. In resistant hypertension with preserved renal function mineralocorticoid receptor antagonists may be useful (208).

In the UKPDS, there was no blood pressure level below which risk of developing moderately elevated albuminuria or beyond increased, i.e., no “J” shape (209). The ADVANCE study explored the effects of reduction of blood pressure below the currently recommended targets of 130/80 mmHg in individuals with normal or moderately increased albuminuria and 125/75 mmHg in those with severely increased albuminuria (210). Over 4 years, the risk of kidney events was reduced by 21%, mainly because of reduced risk of developing moderately or severely elevated albuminuria. However, an achieved systolic blood pressure below 120–130 mmHg was associated with increased mortality and ESKD (211). Therefore, extremely tight blood pressure control should be avoided.

DUAL BLOCKADE OF THE RAS

Addition of an ARB to an ACE inhibitor (212, 213) or of the direct renin inhibitor aliskiren to an ARB reduces blood pressure and albuminuria more than each agent individually. However, in the longer term, dual blockade increases the risk of hyperkalemia, hypotension, and acute, irreversible kidney failure (214-217). Hence dual blockade is not recommended.

MINERALOCORTICOID RECEPTOR ANTAGONISM

Prevention of diabetic nephropathy was attempted in the PRIORITY trial including T2D with normoalbuminuria. High risk for progression to CKD/moderately elevated albuminuria was identified with a urinary proteomic based risk score (CKD-273). High risk individuals were randomized to spironolactone or placebo, and although the biomarker predicted progression of kidney disease, spironolactone was not able to reduce progression compared to placebo over three years (218).

Short term studies in established diabetic nephropathy revealed ~30% reduction in albuminuria with the steroidal mineralocorticoid receptor antagonists (MRAs) spironolactone or eplerenone (219). Preventing over activation of the mineralocorticoid receptor reduces inflammation and fibrosis, but due to potassium problems, diabetes with kidney disease

became a contraindication for these agents. Non-steroidal MRAs have been developed and may cause less potassium issues. The non-steroidal MRAs esaxerenone and finerenone reduced moderately elevated albuminuria in T2D in short term studies with a good safety profile with very little hyperkalemia (220, 221). This led to two large studies testing finerenone in T2D with CKD.

FIDELIO-DKD tested finerenone on a background or RAS blockade with an angiotensin converting enzyme inhibitor (ACEi) or ARB and included 5734 subjects with relatively advanced CKD and T2D (UACR ≥30–≤5000 mg/g, eGFR ≥25–<75 mL/min/1.73 m^2 and the primary endpoint (kidney failure, sustained decrease of eGFR ≥40% or kidney death) was reduced with a hazard rate (HR) 0.82 (95%CI 0.73-0.93, p=0.001). The key secondary outcome (cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure) was also reduced (HR: 0.86; 95% CI 0.75–0.99; *p*=0.03). The incidence of hyperkalemia-related treatment discontinuation was rare, but higher with finerenone than placebo (2.3% and 0.9%, respectively) (222).

FIGARO-DKD also tested finerenone, but included patients with T2D with less advanced CKD, including a greater number of patients with albuminuria in the range 30-300 and impaired eGFR or albuminuria >300 with normal eGFR. FIGARO-DKD was a randomized double-blind phase III study of CV morbidity and mortality, and the primary endpoint was time to first occurrence of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, or hospitalization for HF. The key secondary composite outcome was time to kidney failure, sustained ≥40% decrease in eGFR from baseline, or renal death (223). The study randomized 7437 patients, and the results demonstrated a significant reduction in the primary CV composite endpoint with finerenone compared with placebo (HR: 0.87; 95% CI, 0.76–0.98; *P* = 0.03). The effect on the ≥40% kidney composite endpoint was not significant with finerenone versus placebo (HR: 0.87; 95% CI, 0.76–1.01 *P* = 0.07) (223). However, the standard kidney composite endpoint with a ≥57% decline in eGFR (equivalent to doubling of serum creatinine) instead of the ≥40% decline in eGFR was significantly reduced with finerenone compared with placebo (HR: 0.77; 95% CI, 0.60–0.99; *P* = 0.04) (223).

Finerenone has now been approved for treatment of CKD in T2D by FDA, and will thus be a new opportunity for treatment of diabetic nephropathy. It is not clear where finerenone will be placed in guidelines compared to SGLT2i, but a subgroup analysis from FIDELIOIO-DKD suggest that finerenone is just as efficient when added to SGLT2i and thus it will be interesting to study if the combination provides added benefit (224).

SODIUM INTAKE

Short-term dietary sodium restriction (target sodium intake 50 mmol or 1150 mg Na^+ per day), added to RAS blockade, reduces albuminuria (225). The treatment effects of ARB are greater in patients with lower rather than higher dietary sodium intake (226). Hence dietary counselling to reduce sodium intake is essential and an intake of <2 g of sodium per day (or <90 mmol or 2070 mg of sodium per day, or <5 g of sodium chloride per day) is recommended (179).

NON-CLASSICAL DIABETIC KIDNEY DISEASE

There is no specific evidence for the use of RAS inhibition in individuals without albuminuria. However, control of blood pressure remains crucial to slow progression. Ongoing studies are investigating the effect of the SGLT2 inhibitor empagliflozin on CKD

including low eGFR (20-45 ml/min/1.73m^2) but normal urinary albumin excretion (227).

Endothelin Receptor Antagonists

Atrasentan is an endothelin receptor A antagonist which demonstrated ability to lower proteinuria without significant edema (228). Previously edema had been a concern with this class of agents (229). The SONAR study tested atrasentan in T2D with severely increased albuminuria with progression of kidney disease, ESKD and mortality as the primary outcome (230). Although stopped early for concern of futility, the study eventually showed a kidney benefit of the same magnitude as with the SGLT inhibitors, but without effect on major adverse cardiovascular events and with a tendency to increased risk of heart failure. The primary endpoint was a composite of doubling of serum creatinine (sustained for ≥30 days) or end-stage kidney disease (eGFR <15 mL/min per 1.73 m^2 sustained for ≥90 days, chronic dialysis for ≥90 days, kidney transplantation, or death from kidney failure). The hazard ratio for atrasentan compared to placebo was 0.65 (95% CI 0.49 to 0.88) p=0·0047). The mode of action may relate to an effect on inflammation, but also an effect on podocytes and endothelium and glycocalyx has been proposed from experimental data (231).

Low-Protein Diet

A meta-analysis concluded that a low protein diet significantly improves GFR but not albuminuria, across all subtypes of diabetes and stages of nephropathy (232). A randomized trial of 82 patients with T1D,, severely increased proteinuria and progressive loss of kidney function demonstrated reduced mortality and ESKD (relative risk 0.23; 95% CI 0.07 to 0.72) for patients assigned to a low-protein diet targeting 0.8 g protein/kg body weight/day compared to usual diet (233). Protein intake should not be restricted to less than 0.7 g protein/kg body weight/day because of concerns about malnutrition in ESKD. In line with recommendations for the general population a protein intake of 0.8 g protein/kg body weight/day is recommended for diabetes and CKD, except for people on peritoneal dialysis where a higher intake (1.0-1.2 g protein/kg body weight/day is recommended (179).

Lipids

In diabetic nephropathy lipid lowering medications are recommended to reduce the risk for CVD. There is some evidence that lipid-lowering agents are beneficial to the kidney. In a post hoc analysis of the Collaborative Atorvastatin Diabetes Study, the rate of decline of eGFR was significantly less in those individuals taking atorvastatin 10 mg daily compared with placebo. Fibrates also reduce albuminuria, although they reversibly increase serum creatinine (234).

Cardiovascular Risk—Other Factors

Smoking increases the likelihood for development of diabetic nephropathy as discussed above. There have been no good trials of smoking cessation. However, smoking cessation should clearly be encouraged. There are no studies in diabetic kidney disease with aspirin evaluating long term benefits although short term studies suggest no effect on urinary albumin excretion or GFR (235). In many individuals with established CVD or high risk for CVD aspirin should be considered for prevention of cardiovascular events. There is an increased risk for atrial fibrillation in diabetes and in CKD, and higher morbidity and mortality associated with thromboembolic events including stroke in diabetes with atrial fibrillation (236). In diabetes with atrial fibrillation anticoagulation is

often recommended, and direct oral anticoagulants are usually preferred compared to vitamin K antagonists. In addition to a reduced risk for bleeding and similar or better effects on reducing risk for thrombosis, observational studies suggest reduction in progression of CKD. Thus, a recent study using a health claim database included patients with nonvalvular atrial fibrillation and diabetes that newly initiated rivaroxaban (N=10,017) or warfarin (N=11,665) (237). Patients were matched using propensity scores. In comparison to warfarin, rivaroxaban was associated with lower risks of acute kidney injury events (HR: 0.83; 95% CI, 0.74 to 0.92) and development of stage 5 CKD or need for hemodialysis (HR: 0.82; 95% CI, 0.70 to 0.96) (237). The mechanism could be reduced vascular calcification but needs to be confirmed in randomized controlled trials.

Weight Loss

In a trial comparing intensive lifestyle intervention with diabetes support and education in T2D, individuals randomized to intensive lifestyle modification were less likely to develop CKD over 8 years (238). The effect was partly attributable to reductions in body weight, HbA1c, and systolic blood pressure. Low carbohydrate, Mediterranean, and low-fat diets have similar beneficial effects on change in eGFR and albuminuria over 2 years (239). In individuals with T2D who have undergone bariatric surgery, moderately and severely increased albuminuria regresses to normoalbuminuria (240). Similar benefits were described in a 5-year study in severely obese adolescents with and without T2D (241).

FURTHER MANAGEMENT OF CHRONIC KIDNEY DISEASE STAGE 3 OR POORER

Monitoring Anemia and Bone Chemistry

In progressive CKD from stage 3 onwards, bone chemistry, full blood count, and iron stores should be assessed every 3–6 months.

Monitoring Glucose Control

Red blood cell and protein turnover are abnormal in CKD, making the interpretation of HbA1c, glycated albumin, and fructosamine results difficult, particularly in subjects with CKD 4+. Thus, more reliance should be placed on self-monitoring of blood glucose and continuous glucose monitoring, particularly if treatment can cause hypoglycemia (179).

With declining kidney function, it is important to be aware of the increased risk for hypoglycemia. The glycemic target may have to be increased to avoid hypoglycemic episodes (179) and glucose lowering agents may have to be changed or have their dose adjusted (Table 5). There are several explanations for this: a) the kidney is important for the metabolism of many glucose lowering medications and this function is impaired in advanced CKD; b) the kidney contributes to total endogenous glucose production by approximately 30% which declines with loss of kidney function; c) in advanced CKD acidosis affects the liver's ability to produce glucose and compensate for failing kidney gluconeogenesis, and malnutrition and muscle wasting contributes to the risk for hypoglycemia; d) people with diabetic nephropathy are often older, have longer diabetes duration, and more frequently suffer from comorbidities, especially cardiovascular disease, and are thus more likely to be on multiple medications with can have potential interactions with glucose lowering medications (242).

Table 5. Glucose-Lowering Agents in Chronic Kidney Disease	
Drug	**Comment**
Metformin	Risk of accumulation and possibly lactic acidosis Caution when eGFR <45 mL/min/1.73 m^2 Stop when eGFR <30 mL/min/1.73 m^2
Sulfonylureas	Glibenclamide, gliclazide, and tolbutamide predominantly renally excreted; may need to reduce dose
Meglitinides	~10% excreted via kidney; usually safe
Thiazolidinediones	Predominantly hepatic metabolism; use may be limited by fluid retention
Dipeptidyl peptidase IV inhibitors	Dose may need to be reduced in some agents
Glucagon-like peptide-1 receptor agonists	Few data when eGFR <15 mL/min/1.73 m^2
Sodium–glucose co-transporter 2 inhibitors	Protect kidney and heart down to eGFR>25, but ineffective at reducing glucose at eGFR <45 mL/min/1.73 m^2
Insulin	Excreted by kidney; may need to reduce dose and/or switch to shorter-acting preparations

Metformin and its metabolites are excreted mainly by the kidney. In kidney failure, they accumulate and inhibit lactate oxidation. Metformin should therefore be used cautiously in those with eGFR <45 mL/min/1.73 m^2, and stopped completely when eGFR <30 mL/min/1.73 m^2 (243).

The sulfonylureas glibenclamide, gliclazide, and tolbutamide are excreted predominantly by the kidneys and accumulate in CKD. Their dose, and indeed the dose of any sulfonylurea, may need to be reduced as CKD progresses. Only ~10% of the meglitinides, repaglinide and nateglinide, are excreted by the kidneys, making them suitable alternative agents. The thiazolidinediones, rosiglitazone and pioglitazone, are predominantly metabolized in the liver. However, their use in ESKD may be limited by fluid retention.

Insulin is also excreted by the kidney so that reduced dosage, and perhaps a switch to shorter acting preparations, may be required.

The dose of some but not all DPP-4 inhibitors and GLP-1 receptor agonists may need to be reduced as kidney function deteriorates. The SGLT-2 inhibitors become less effective at decreasing glucose levels as GFR falls.

Anemia

Anemia is common in people with diabetes and CKD stage 3 or poorer (244). Full investigation of iron deficiency anemia may be needed to exclude a non-kidney cause. Those with anemia have a higher mortality, higher rates of hospital admission with heart failure, and poorer quality of life. Iron stores should be

repleted with oral or parenteral iron as necessary, and erythropoietin replacement commenced if indicated. In the TREAT trial it was investigated if treatment of anemia in T2D with CKD would improve renal or cardiovascular outcome, but the trial showed no benefit (245).

When to Refer to Nephrology

Patients who begin dialysis as an emergency do less well than those in whom treatment is planned (246). Referral to nephrology should be made when eGFR is declining rapidly (>5 mL/min/1.73m^2/year or when eGFR is <30-45 mL/min/1.73 m^2. This allows structured physical and psychological preparation for kidney replacement therapy. Earlier referral may be necessary in particular circumstances (Table 6). The need for kidney replacement therapy should be discussed with all patients and those who wish it should have access. People without significant comorbidities will usually be offered transplantation. Full cardiovascular assessment and treatment are essential before transplantation.

Table 6. Indications for Referral to Nephrology
Diagnosis uncertain
Hypertension difficult to control
Fluid overload
Anemia unresponsive to oral iron
Abnormal bone chemistry (calcium, phosphorus, PTH)
eGFR 30–45 mL/min/1.73 m^2
Nephrotic syndrome
eGFR fall >5 mL/min/1.73 m^2 per year

Organization of Care

Structured care, delivered by trained specialists working with clear protocols with specific, multiple treatment goals for all the variables described above, reduces the incidence of moderately elevated albuminuria (247, 248) and provides greater kidney and cardiovascular benefits than routine care for individuals with T2D and CKD (179, 249, 250). Progression to ESKD or death, need for laser therapy for management of retinopathy, and cardiovascular endpoints including stroke and heart failure are all reduced by such multifactorial interventions (251-254). When structured intensive multifactorial intervention targeting lifestyle factors (diet, exercise, smoking) and heart and kidney risk factors (blood glucose, blood pressure, lipid management) compared to usual care was started already in T2D with moderately elevated albuminuria, long-term follow-up of the Steno-2 study demonstrated that eight years of intervention translated into almost 8 years of extended median survival (Figure 11) (251).

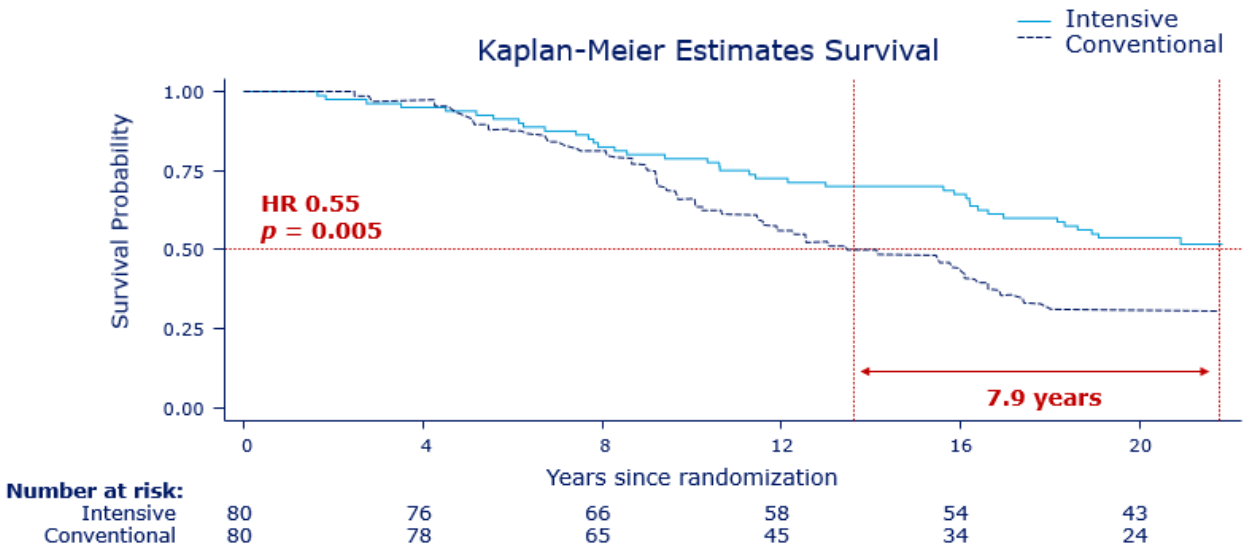

Figure 11. Steno-2 post-trial: Twenty-one years sustained effect of intensive multifactorial intervention compared to standard of care for 8 years targeting lifestyle and heart and kidney risk factors.

Pregnancy in Women with Diabetes and Chronic Kidney Disease

Women with diabetic nephropathy have poor pregnancy outcomes (255). They remain at increased risk of hypertension, preeclampsia, abnormal fetal growth, and preterm delivery (256). In a recent series, the prevalence of diabetic nephropathy and moderately elevated albuminuria in early pregnancy was similar in women with T1D or T2D, and pregnancy outcomes were comparable regardless of the type of diabetes (257). Women with any evidence of CKD therefore should be counselled pre-pregnancy. RAS inhibitors should be stopped and therapies safe in pregnancy, such as methyldopa, labetolol, and nifedipine, used as substitutes. In women with T1D, maintenance of BP <135/85 mmHg and proteinuria <300 mg/24 h with methyldopa improves outcomes (208, 258).

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