Risk Factors, Symptoms, Biomarkers, and Stages of Chronic Kidney Disease

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Whereas the symptoms of chronic kidney disease (CKD) in diabetes are few, there are many risk factors and biomarkers that can be used to identify individuals at high risk for development of this complication, and many of these are targets for intervention to prevent or delay the disease. This article describes the risk factors and other markers of CKD and the various stages of the disease.

Risk Factors for CKD in Diabetes

Many factors are associated with CKD in diabetes (**Figure 1**). Associations may be with both albuminuria and glomerular filtration rate (GFR) or with one variable only. Some factors influence initial development of kidney disease and others progression of the disease. Duration of diabetes is one of the strongest risk factors for diabetic nephropathy, but because type 2 diabetes is often silent, CKD may be present at diagnosis of diabetes.

Hyperglycemia

Several studies demonstrate the importance of hyperglycemia in the development and progression of CKD in diabetes (or diabetic kidney disease [DKD]) (43,44). The UK Prospective Diabetes Study documented a progressive beneficial effect of intensive metabolic control on the development of microalbuminuria and overt proteinuria (45), and a 10-year post-study follow-up demonstrated long-lasting benefit, which was termed a "legacy effect" (46).

Greater variability in A1C is associated independently with albuminuria and diabetic nephropathy (47,48). The beneficial effect of improved glycemic control was confirmed in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron

Modified Release Controlled Evaluation) trial, in which 11,140 patients with type 2 diabetes were followed and a 21% reduction (95% CI 7–34%) in development of nephropathy was seen in patients randomly assigned to strict glycemic control (49). Even end-stage renal disease (ESRD) was reduced in the ADVANCE trial, although it was a very rare event (50).

Overall, it has been difficult to demonstrate the benefit of improving glycemic control on established CKD in type 2 diabetes, in contrast to the benefit on development of CKD. Recent studies with glucose-lowering agents such as glucagon-like peptide 1 receptor agonists found reduced progression of albuminuria and loss of kidney function (51,52). Sodium–glucose cotransporter 2 (SGLT2) inhibitors in particular have demonstrated benefit on progression of albuminuria, decline in kidney function, and development of kidney failure; but, although the mechanisms are not clear, the reduction in glucose is probably of minor importance (8,53). Thus, SGLT2 inhibitors are even beneficial in people with CKD who do not have diabetes (53).

Blood Pressure

Blood pressure is crucial to the development and progression of CKD in diabetes (44,54,55). The excess prevalence of hypertension in type 1 diabetes is confined to patients with nephropathy (56). Once severely increased albuminuria is present, frank hypertension is present in 80% of individuals and is almost universal in those with ESRD. In type 2 diabetes, the link between hypertension and kidney disease is less striking because hypertension is so common. Almost all patients with moderately elevated or worse albuminuria have hypertension. In people with diabetic nephropathy, variability in systolic blood pressure is independently associated with the development of ESRD (57).

Treatment of blood pressure, particularly with inhibitors of the renin angiotensin system (RAS), has been a standard of care for both prevention and treatment of CKD in diabetes based on studies with angiotensin II receptor blockers in moderately elevated albuminuria (microalbuminuria) and type 2 diabetes (58), as well as in established proteinuria in type 2 diabetes (3,4). Even prevention of CKD has been suggested, at least in hypertensive type 2 diabetes, when treated with RAS-blocking agents (59).

Renin-Angiotensin-Aldosterone System

Several components of the renin-angiotensin-aldosterone system (RAAS) are elevated and considered to contribute to the progression of diabetic nephropathy. Accordingly, blocking the RAAS has been demonstrated to be kidney protective.

FIGURE 1 Putative promoters of CKD progression in diabetes.
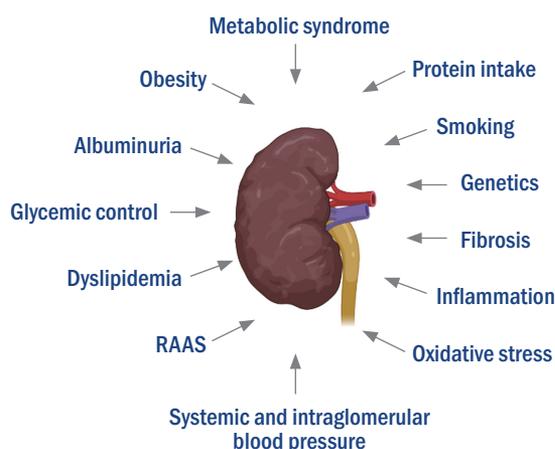
Experimental studies have suggested that succinate, formed by the tricarboxylic acid cycle, provides a direct link between high glucose and renin release in the kidney (60). Focus was initially on the damaging effect of angiotensin II.

As discussed for blood pressure, RAS-blocking agents have been a standard of care in CKD in 20 years. Aldosterone represents another component of the RAAS that should be considered important in the pathophysiology of diabetic nephropathy. Aldosterone is a hormone that, in addition to regulating electrolyte and fluid homeostasis, has widespread actions through genomic and nongenomic effects in both the kidney and tissues not originally considered targets for aldosterone such as the vasculature, central nervous system, and heart (61).

Obesity
Obesity is an increasing problem in the general population and among people with diabetes. Several studies have indicated that severe obesity (BMI >40 kg/m^2) enhances ESRD risk sevenfold (62). Even a BMI >25 kg/m^2 was found to increase ESRD risk (62). This effect is independent of the effects of hypertension and diabetes, the prevalence of which are increased in individuals with obesity. An effect of obesity on renal hemodynamics leading to increased glomerular pressure and hyperfiltration has been suggested as the mechanism (63), and adiponectin was suggested to link obesity to podocyte damage (64). Weight reduction from bariatric surgery (65) or pharmacological treatment (66) has been associated with improved renal outcomes, although large weight reductions will improve estimated GFR (eGFR) and not true GFR because of loss of muscle mass and then decline in serum creatinine (67).

Other Metabolic Factors
Blood lipids, including triglycerides (68,69), contribute to the development and progression of CKD, although the lipid phenotype alters as kidney disease progresses (70–72). Insulin resistance increases the risk of albuminuria in type 2 diabetes (73). Individuals with type 1 or type 2 diabetes and CKD are more likely to have the metabolic syndrome (74–76). Multifactorial intervention targeting lifestyle, glucose, blood pressure, and lipids has a beneficial impact on both cardiovascular and kidney outcomes (77).

Genetic Factors
Genetic factors influence susceptibility to CKD in both type 1 and type 2 diabetes (78,79). If one sibling with type 1 diabetes has nephropathy, the risk to a second sibling is increased four- to eightfold compared to sibling sets in which neither has nephropathy (80). Similar familial clustering has been described in type 2 diabetes (81). Despite these findings, strong and clinically useful genes for CKD in diabetes are still lacking.

The clustering of conventional cardiovascular risk factors and cardiovascular disease (CVD) in people with diabetes and CKD also occurs in their parents (82,83). This finding suggests that the genetic susceptibility to nephropathy also influences the associated CVD.

Multiple genes, either protective or deleterious, are involved. Different loci may influence albuminuria and GFR separately (84). Epigenetic modification may also be important (85).

Ethnicity
Albuminuria and CKD stages 4 and 5 are more common in U.K. Afro-Caribbean and South Asian individuals than White European people (86,87). The prevalence of early CKD (defined as moderately elevated or greater albuminuria and eGFR<60 mL/min/1.73 m^2) is also higher in Latino and African American individuals than in White people (88). Albuminuria and CKD are also more common in Pima Indians (89) and in Māoris and Pacific Islanders (90,91) than in White Europeans. Reasons for this varying prevalence may include differing genetic influences and altered response to, or poorer access to, treatments.

Type 2 Diabetes Developing in Young People
Individuals who develop type 2 diabetes at a young age have a high prevalence of hypertension and moderately elevated albuminuria (92). ESRD and death are particularly common in young people from ethnic minorities (93–95). However, in some of these populations, there is a high prevalence of kidney disease unrelated to diabetes (96).

Albminuria and eGFR
Baseline albuminuria and eGFR independently influence the development and rate of progression of CKD (97,98). Baseline albuminuria strongly predicts ESRD (99). Higher levels of normo-albuminuria (100) and lower eGFR (101) predict a faster decline in eGFR. Conversely, a short-term reduction in albuminuria with intervention is associated with reduced progression of kidney and cardiovascular complications (102,103).

Other Risk Factors
Other risk factors for nephropathy include smoking (98), pre-eclampsia (104), periodontitis (105), obstructive sleep apnea (106), and nonalcoholic fatty liver disease, all of which are independently associated with diabetic nephropathy (107,108).

Symptoms of CKD
Whereas albuminuria is often an early sign of CKD, there is a paucity of symptoms related to CKD in diabetes until late stages, making systematic screening mandatory to detect CKD as early as possible. Edema is often the first symptom, followed by fatigue and other uremic symptoms with pruritus, and then nausea, but this usually does not occur until CKD stage 4 or 5 (**Figure 2**) (109).

Other symptoms relate to complications, including angina from ischemic heart disease, dyspnea resulting from heart failure, aching from painful neuropathy, or typical symptoms of urinary tract infection. Although these complications are frequent, the symptoms may be atypical or weak because of the presence of neuropathy.

FIGURE 2 Stages and prognosis of CKD based on albuminuria and GFR from the KDIGO (Kidney Disease: Improving Global Outcomes) 2012 clinical practice guideline (109). The GFR and albuminuria grid depicts the risk of progression, morbidity, and mortality by color, from best to worst. Green indicates low risk (if no other markers of kidney disease and no CKD), yellow indicates moderately increased risk, orange indicates high risk, and red indicates very high risk. Reprinted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Kidney Int Suppl 2013;3:1–150.

				Persistent Albuminuria Categories, Description and Range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g	30–300 mg/g	>300 mg/g
GFR Categories (mL/min/1.73 m²), Description and Range	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	🟥	🟥	🟥

Markers from Different Pathways Predict Kidney Outcomes

Progression of CKD is related to increased activity in different pathophysiological pathways that is reflected in biomarkers of these processes (**Figure 3**) (110).

Vascular Damage

Elevated urinary albumin excretion reflects widespread vascular damage and predicts development of kidney failure and cardiovascular events. In addition, treatment-induced reductions are associated with improved kidney and cardiac prognosis, as initially demonstrated in smaller studies (102,111) and recently documented in meta-analyses of observational (112) and intervention (103) studies.

Troponin T, in addition to its use in acute settings as a marker of myocardial damage, has been used to demonstrate vascular, cardiac, and kidney risk and could be a marker of increased risk for atherosclerosis (113,114).

Fibrosis

Different markers of fibrosis have been studied such as serum and urine PRO-C6, a C-terminal pro-peptide generated during collagen VI formation. In people with type 2 diabetes and microalbuminuria, a doubling of serum PRO-C6 increased hazards for cardiovascular events (hazard ratio [HR] 3.06, 95% CI 1.31–7.14), all-cause mortality (HR 6.91, 95% CI 2.96–16.11), and reduction of eGFR of >30% (HR 4.81, 95% CI 1.92–12.01).
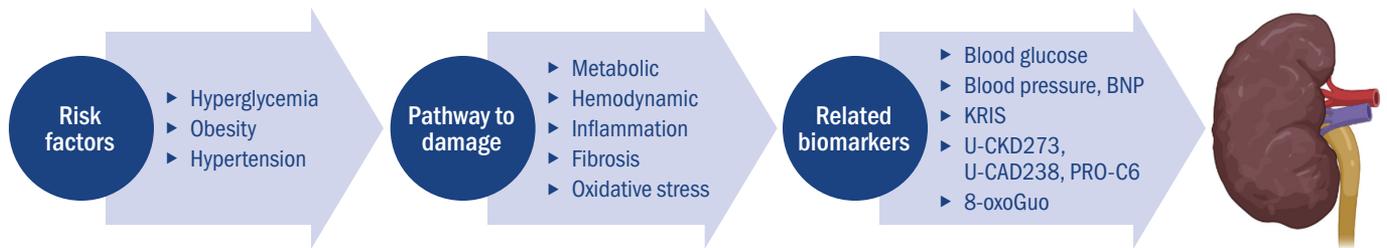
Applying urinary proteomic analysis with capillary electrophoresis coupled to mass spectrometry, Good et al. (115) described a high-dimensional urinary biomarker pattern composed of 273 peptides associated with overt kidney disease: CKD273. The original studies included people with CKD on a mixed background compared to healthy control subjects. The components of CKD273 include collagen fragments and are assumed to relate to early fibrosis in the kidney. In retrospective studies, this proteomic classifier identified subjects at risk for CKD and progression in albuminuria class earlier than the indices currently used in clinical practice (116). In a prospective study including people with type 2 diabetes and normoalbuminuria, it was also demonstrated that CKD273 was associated with development of microalbuminuria and impaired kidney function (117).

Inflammation

Multiple markers have been investigated related to inflammation. These include fibrinogen, interleukin 6, and tumor necrosis factor-α (TNF-α), which were found to be associated with risk of CKD progression (118). Some of the most widely studied markers have been tumor necrosis factor receptors (TNFRs) 1 and 2. Recently, a Kidney Risk Inflammatory Signature was developed with 17 inflammatory markers, including TNFR superfamily members (119). The signature was tested in two cohorts as a marker of ESRD in both type 1 and type 2 diabetes. All components of the signature had a systemic, non-kidney source and may guide therapy to new targets. Interestingly, the signature was improved with the anti-inflammatory agent baricitinib, but not with RAS blockade (119).

FIGURE 3 Pathways and biomarkers of CKD. BNP, brain natriuretic peptide; KRIS, kidney risk inflammatory signature; U-CAD238, urinary proteome-based classifer for coronary artery disease 238 ; U-CKD273, urinary proteome-based classifer for chronic kidney disease 273. Adapted from Rossing P, Persson F, Frimodt-Moller M, Hansen TW. Diabetes 2021;70:39–50.

Risk factors	Pathway to damage	Related biomarkers
▸ Hyperglycemia ▸ Obesity ▸ Hypertension	▸ Metabolic ▸ Hemodynamic ▸ Inflammation ▸ Fibrosis ▸ Oxidative stress	▸ Blood glucose ▸ Blood pressure, BNP ▸ KRIS ▸ U-CKD273, U-CAD238, PRO-C6 ▸ 8-oxoGuo

Oxidative Stress

It has been proposed that elevated levels of uric acid induce vascular and kidney damage, hypertension, and atherosclerosis due to inflammation and oxidative stress. Elevated uric acid levels were associated with cardiovascular events and progression of kidney disease in type 1 diabetes (120). The PERL (Prevention of Early Renal Function Loss) study (121) tested whether lowering uric acid with allopurinol in people with type 1 diabetes and early CKD with albuminuria or declining eGFR could prevent loss of measured GFR over 3 years. Mean serum urate level decreased from 6.1 to 3.9 mg/dL with allopurinol and remained at 6.1 mg/dL with placebo. Despite this lowering, the trial found no evidence of a kidney protective effect on albuminuria or decline in GFR. These results suggest that uric acid is not a target, in line with a Mendelian randomization study in type 1 diabetes (122). However, a study was presented in 2019 with greater reduction of uric acid in a small group of people with type 2 diabetes who were followed for 24 weeks taking the urate reabsorption inhibitor verinurad and the xanthine oxidase inhibitor feboxustat in combination, resulting in a 49% reduction in urine albumin-to-creatinine ratio (ACR) compared to placebo (123).

Other markers of oxidative stress are oxidatively modified guanine nucleosides 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) and 8-oxo-7,8-dihydroguanosine (8-oxoGuo) excreted in the urine. The level of 8-oxoGuo was associated with mortality and CVD in type 2 diabetes (124).

Transcriptomics

Tissue from kidney biopsies may provide diagnostic information with typical histological findings. More recently, it has been suggested that histological and transcriptomic analysis of kidney tissue may be relevant to characterize fast CKD progressors and select optimal treatments (125). Transcriptomic profiles in kidney tissue from patients with DKD and animal models of DKD have suggested the importance of the Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway as a key pathway in DKD. A clinical study in diabetes intervening with a JAK-STAT inhibitor subsequently demonstrated reduced albuminuria (126).

Metabolomics

Metabolites have been investigated in blood and urine using platforms that capture hundreds or even thousands of metabolites. So far, there have only been a few studies in people with type 2 diabetes and CKD. Pena et al. (127) demonstrated that a few metabolites in serum and urine could improve prediction of progression in albuminuria status in type 2 diabetes, and Solini et al. (128) demonstrated in patients with type 2 diabetes that serum, but not urine, metabolites could improve prediction of progression of albuminuria and decline in GFR. Sharma et al. (129) described a signature of 13 metabolites in urine that pointed toward mitochondrial dysfunction as a key feature in progression of CKD in diabetes. Niewczas et al. (130) demonstrated that uremic solutes were associated with the development of ESRD in people with type 2 diabetes. Both the metabolome and lipidome were recently studied in type 1 diabetes (72,131). A number of markers of progression of CKD were identified but await confirmation, which is often a problem, as different studies use diverse platforms.

Stages of CKD

CKD in diabetes is defined as the presence of persistently elevated albuminuria of >30 mg/24 hour or a urinary ACR >30 mg/g creatinine, confirmed in at least two out of three samples (132). As such, its diagnosis is clinical, requiring little more than basic clinical and laboratory evaluations. The normal range for albuminuria is <30 mg/g. The presence of moderately elevated albuminuria (microalbuminuria) (30–299 mg/g) is widely regarded as a precursor of more advanced stages of CKD and a marker of vascular damage. However, in some cases, elevated albuminuria can display remission either spontaneously or as a result of treatment (133–135). Remission indicates lower kidney risk compared to progression of albuminuria. The Italian RIACE (Renal Insufficiency and Cardiovascular Events) study (136) of >15,000 people with type 2 diabetes suggested that patients with elevated albuminuria display the typical microvascular phenotype, whereas nonalbuminuric subjects with impaired kidney function had a more cardiovascular or macrovascular phenotype.

For CKD in general, including in people with diabetes, it has been recommended to stage the severity using a combination of etiology (if known), level of urinary albumin excretion, and eGFR (**Figure 2**) (109).

Conclusion

Advances in diagnosis and treatment have provided new options and potential for better outcomes for CKD in diabetes. As treatment opportunities continue to expand, biomarkers and, most likely, combinations of biomarkers will help us select the optimal treatment or combination of treatments for each patient. This ability will ensure better outcomes and reduce adverse events and unnecessary polypharmacy. A more detailed approach applying multiple biomarkers to select the right treatment for the right person may seem complicated and costly initially but has the potential to save both patients and the health care system considerable costs (137). Integrating multiple "-omics" platforms may lead to a much deeper understanding of the disease. Hopefully, such an approach will help to prevent CKD in diabetes and improve kidney outcomes in the future. For now, much can already be achieved if we ensure full integration of the use of simple biomarkers such as albuminuria and eGFR (138).

See references starting on p. 34.

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