1 Factors beyond diabetes facilitating the development and evolution of diabetic nephropathy

Diego F. Márquez, Luis M. Ruilope

INTRODUCTION

Chronic kidney disease (CKD) affects between 10.5% to 15% of the adult American population.[1, 2] It is important to note that most of the CKD population is at increased risk of cardiovascular (CV) events, which include progression to end stage kidney disease (ESKD) or cardiac or cerebrovascular events. One of the main challenges is that kidney disease is typically asymptomatic, particularly at stage 3, where the possibility of a CV event, particularly ischemic cardiopathy is the leading cause of death. Patients who progress to 4 or 5 of CKD are more likely to reach ESKD.[3, 4]

Over the last decade, efforts have been made to improve our understanding of CKD progression, focusing on epidemiology, pathophysiology, and molecular aspects, to reduce the burden of CKD and its complications. Previous epidemiological studies have identified several risk factors for CKD progression, categorized as initiating or perpetuating factors.[5] We will describe risk factors associated with CKD progression (**Table 1.I**).[6-40]

Initiating factors play a role in starting the cycle of nephron loss or nephropenia,[17] such as older age, male sex, nephron number, acute kidney injury (AKI) episodes, diabetes metabolic control, and perpetuating factors such as proteinuria, hyperfiltration, hypertension and metabolic control (uric acid, glycated hemoglobin) that sustain the damage. Some genes (in particular, *APOL-1*) have been associated with a worse prognosis.[17]

Table 1.I. Risk factors associated with CKD progression.

Risk factor	Findings/association
Age	Advanced age has been associated with increased risk of progression of DKD.[6] Nevertheless, studies have yielded contradictory results regarding the correlation between older age and progression of CKD.[7-9]
Sex disparities	Being male was associated with increased risk of progression of DKD.[10, 11]
	Women have lower risk of kidney failure, all-cause mortality, and cardiovascular mortality compared to men.[12]

(To be continued)

TABLE 1.1. Risk factors associated with CKD progression (*continues*).

Risk factor	Findings/association
Ethnic disparities/genetic factors	Hispanic and non-Hispanic Black individuals have higher rate of kidney failure compared to non-Hispanic White individuals.[13]
	Black patients carrying *APOL1* gene at higher risk of CKD progression and composite renal outcomes.[14, 15]
Smoking status	Current smoking is associated with increased risk of CKD progression.[16]
Diabetic *vs.* non-diabetic CKD	CKD patients with diabetes have 2.75 times increased risk of progressing to dialysis compared to those without diabetes.[17, 18]
Hyperglycemia	Intensive glucose control was associated with reduced risk of developing DKD.[19, 20]
	However, the ACCORD study found that intensive glucose control increased mortality and did not reduce major cardiovascular events.[19]
Lipid profile	Some results showed disparities in this field. Total cholesterol level predicts a greater decline in measured GFR as well as high serum triglyceride levels. Intervention trials did not show benefits in eGFR but reduced major CV end points.[9, 21, 22]
Diet	Higher urinary sodium excretion was associated with increased risks of CKD progression and all-cause mortality.[23] Sodium bicarbonate supplementation also reduced the progression of CKD.[24, 25]
Uric acid	Elevated UA levels independently predict the development of CKD.[26, 27] However, recent clinical trials did not show benefits in terms of kidney outcomes with UA reduction.[28, 29]
Hypertension	Resistant HTN is common among CKD patients.[30, 31] Uncontrolled hypertension in CKD patients worsens the decline in GFR.[32] RASi is mandatory in CKD, but discontinuing RASi in advanced CKD patients should be avoided.[33, 34]
Arterial stiffness	Patients in the highest tertile of PWV (>10.3 m/s) had a higher risk of developing ESKD, ESKD or a significant decline in estimated glomerular filtration rate, and death.[35]
	PWV, which reflects arterial stiffness and calcification, may have a role in risk stratification among CKD patients.[36]
Atrial Fibrillation	The prevalence of AF in the CKD population is elevated.[10] Incident AF was associated with a three-fold higher risk of kidney failure.[37]
Albuminuric and non-albuminuric CKD	Non-albuminuric DKD affects up to 36% of patients[38] and was associated with a slower decline in eGFR compared to albuminuric patients However non-albuminuric CKD patients still carried a higher risk of death and major adverse CV events.[39, 40]

eGFR: estimated glomerular filtration rate; DKD: diabetic kidney disease; UA: uric acid; CKD: chronic kidney disease; ESKD: end-stage kidney disease; HNT: hypertension; RASi: renin angiotensin system inhibitors; PWV: pulse wave velocity; AF: atrial fibrillation; CV: cardiovascular.

Numerous risk factors contribute to the natural course of CKD. It is crucial to understand their contribution to CKD progression.[7] In this chapter, we will describe and discuss some of these factors.

AGE

Previous studies have indicated that the annual decline in eGFR is approximately 1 mL/min/1.74 m^2 per year after the age of 40.[41]

Older age has been identified as a risk factor for the progression of diabetic kidney disease (DKD) in some studies, but others have associated this risk with the physiological decline of GFR that typically occurs around the age of 40. Furthermore, earlier onset of type 2 diabetes mellitus in younger patients has been shown to increase the future risk of developing DKD.[6]

The association between older age and CKD progression has been demonstrated in various studies involving patients with DKD. However, there are conflicting findings in other studies that do not establish this association.[7-9]

SEX DISPARITIES

Sex-specific differences have been observed in the progression and mortality of CKD. Several studies have reported that being male is a risk factor for the progression of diabetic kidney disease (DKD).[7]

According to the United States Renal Data System, despite a higher prevalence of CKD in women, the prevalence of kidney failure is greater in men, suggesting that women may experience a slower decline in kidney function compared to men.[10, 42-44] Regression analysis has indicated that women have a 28% lower risk of kidney failure compared to men.[11] One possible explanation for this disparity is the protective effect of endogenous estrogens.[45]

Furthermore, the higher risk of renal events in men may – partially – be attributed to higher levels of proteinuria compared to women.[46] In a study that linked albuminuria with CKD progression, it was found that women were more likely to follow the non-albuminuric pathway.[47]

A recent Swedish study involving 35,080 CKD patients demonstrated that women have reduced risk for CKD progression (subhazard ratio [SHR]: 0.88; 95% confidence interval [CI]: 0.85-0.92), as well as lower risk of all-cause (SHR: 0.90 [95% CI: 0.85-0.94]) and cardiovascular (SHR: 0.83 [95% CI: 0.76-0.90]) mortality compared to men.[12]

Based on the available evidence, it can be concluded that men have a higher rate of all-cause and CV mortality, an increased risk of CKD progression, and a steeper decline in eGFR compared to women. However, it is important to consider individual patient characteristics and other factors when assessing the risk and progression of CKD in both men and women.

ETHNIC DISPARITIES/GENETIC FACTORS

The Chronic Renal Insufficiency Cohort (CRIC) Study, established by the National Institute of Diabetes and Kidney Disease is a large-scale study that evaluates the outcomes of diabetic and non-diabetic CKD patients in different phases.[10]

An epidemiological study within the CRIC Study examined ethnic disparities in CKD outcomes over a median follow-up of 6.6 years.[13] It was found that Hispanic and non-Hispanic Black individuals experienced an almost two-fold higher rate of kidney failure compared with non-Hispanic White individuals. However, in multivariable analysis using death as a competing risk, the risk of kidney failure was found to be similar between Hispanic and non-Hispanic White individuals (hazard ratio [HR]: 1.32; 95% CI: 0.96 to 1.81), as well as between Hispanic compared with non-Hispanic Black individuals (HR 0.94;95% CI 0.71 to 1.25).[13]

In a retrospective British study involving 3855 patients with type 1 diabetes mellitus or type 2 diabetes mellitus, it was reported that individuals of Black or South Asian ethnicity exhibited a more rapid rate of decline in GFR compared to those of Caucasian ethnicity.[48] Additionally, Elley *et al.* found that individuals of Pacific Islander and Maori descent had higher rates of disease progression compared to those of European descendants.[49] These ethnic disparities have important implications and may be influenced by a complex interplay of economic, social, and educational factors, as well as modifiable risk factors.[10]

A special consideration must be given to the African American population, as they are at an increased risk for ESKD compared to withe patients. The *APOL1* gene has been implicated in the higher risk of CKD progression observed among African American individuals.[14] Black patients carrying the *APOL1* gene, are at higher risk of rapid GFR decline and a greater risk of composite renal outcomes compared to white patients, both in individuals with diabetes and those without diabetes (P<0.001 for all comparisons).[15]

SMOKING STATUS

Several studies have demonstrated a positive association between smoking status and CKD. Many of these studies have specifically investigated the impact of current smoking status in individuals with type 2 diabetes mellitus.[50, 51] In a study conducted by Ricardo *et al.*, involving 3006 participants, it was found that individuals who had previously or had never smoked had a reduced risk of CKD progression compared to current smokers (HR 0.75; 95% CI 0.58 to 0.97), and a reduced risk of atherosclerotic events (HR 0.55; 95% CI: 0.40-0.75 *vs.* current smoker).[16]

DIABETIC VS. NON-DIABETIC CKD

Previous studies have demonstrated that diabetes nephropathy is associated with an increased risk for CV events. The rate of CKD progression to ESKD in patients with DM has remained unchanged over the past two decades, with approximately 25 of 10,000 adults

with DM developing ESKD per year.[3] Among patients without diabetes and those with diabetes, the mean eGFR slope was reported as -1.4±3.3 and -2.7±4.7 mL/min/1.74 m^2 per year, respectively.[17]

CKD patients with diabetes have 2.75 times increased risk (95% CI: 1.70-4.46) of progressing to dialysis, compared to those without diabetes.[18] The onset of diabetes mellitus leads to glomerular hyperfiltration and sodium-glucose cotransporter 2 (SGLT2)-driven deactivation of tubuloglomerular feedback. It is important to consider patients with previous non-diabetic CKD who subsequently develop diabetes. In these individuals, prior nephron loss (nephropenia) before the onset of diabetes implies an earlier increase in single nephron glomerular filtration rate. After the onset of diabetes, the effects of DKD on the kidneys further accelerate the process of hyperfiltration and generate sclerosis in kidneys with pre-existing damage.[5]

HYPERGLYCEMIA

Glycemic control is essential to decrease target organ damage generated by diabetes mellitus. Different trials were done to evaluate the association of glycosylated hemoglobin (HbA1c) and kidney damage. In addition, different intervention trials of intensive glucose control were Hyperglycemia plays a significant role in generating target organ damage in DM, making glycemic control essential. Various trials have been conducted to evaluate the association between HbA1c levels and kidney damage, as well as interventions for intensive glucose control.

Hyperglycemia plays a significant role in generating target organ damage in diabetes mellitus, making glycemic control essential. Various trials have been conducted to evaluate the association between intensive glucose control and CV and renal end points. Two landmark trials involving patients with early-stage type 1 or type 2 DM demonstrated that early intensive blood glucose control had long-lasting favorable effects on the risk of developing DKD.[52, 53] Intensive glucose control targeting an HbA1c level ≤7% reduced the 9-year risk of developing microalbuminuria and macroalbuminuria by 34% and 56% respectively, in patients with type 1 diabetes compared to the standard of care.[19] Similar results were observed in patients with recent diagnosis of diabetes. Holmann *et al.* showed that after 10 years of intensive glucose control (HbA1c 7%), there was a 24% reduction in the development of microvascular complications compared to conventional therapy.[20]

Furthermore, Trivin *et al.*, published interesting findings in a CKD cohort with prediabetes. They found that HbA1c values in the prediabetes range were associated with mortality, although there was no association with end-stage renal disease (ESKD) risk after adjusting for CKD progression risk factors.[54]

However, the ACCORD study,[19] which included patients with type 2 diabetes, compared intensive treatment (HbA1c <6%) with standard treatment (HbA1c 7-7.9%) in 10252 patients. The study concluded that compared to standard therapy, the use of intensive therapy to target normal HbA1c levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. It is possible that the glycemic changes induced by hyperglycemia are responsible for future target organ damage, which often becomes irreversible. Therefore, ear-

ly, and vigorous treatment in patients with DM is crucial to protect against future kidney and vascular damage. Some authors have referred to this phenomenon as "metabolic memory."[55] Overall, early diagnosis of dysglycemia provides an opportunity for healthcare professionals and patients to work together in managing blood glucose levels effectively. By intervening early and optimizing glycemic control, the risk of complications can be minimized.

LIPID PROFILE

Although traditional CV risk factors are highly prevalent in individuals with CKD, these patients have often been excluded from studies targeting the modification of these factors. Lipid-lowering therapies have shown to improve CV outcomes in non-dialysis-dependent CKD patients, but their effectiveness in dialysis-dependent patients is less clear. Several studies have investigated the association between lipid profiles and CKD progression, yielding disparate results. In patients with type 2 DM, Altemtam *et al.* reported an association between high serum triglyceride levels and decline in eGFR, but it is possible that this hypertriglyceridemia was secondary to poor glycemic control.[9]

Other studies have found that total cholesterol levels predict greater decline in measured GFR.[21] Chang *et al.* reported an association between higher triglyceride levels, lower high-density lipoprotein cholesterol (HDL-C), and the development of albuminuria endpoints, but no association with higher low-density lipoprotein cholesterol (LDL-C).[22] However, some results in this field have generated confusion. For instance, HDL-C, which is typically considered vascular-protective, may be altered, and could potentially cause endothelial dysfunction in patients with CKD.[56-58]

Nonetheless, there are intervention studies that have demonstrated renal protection using statins and ezetimibe in CKD patients. The Study of Heart and Renal Protection (SHARP) study was a randomized double-blind placebo control trial, that randomized 4650 patients to receive a combination of simvastatin plus ezetimibe, and 4620 patients to received placebo. Authors concluded that in patients with advanced CKD, reduction of LDL cholesterol with simvastatin 20 mg plus ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events. By the meantime, CKD population is at highest CV risk, and the use of statins are recommended by guidelines as part of the treatment.

DIET

Healthy dietary patterns have consistently shown associations with a reduced risk of CKD progression. He *et al.* conducted a study evaluating the effect of dietary sodium and potassium on CKD progression using 24-hour urine measurements.[59] The study found that individuals with higher urinary sodium excretion (≥195 mmol per 24 hours) were more likely to experience CKD progression compared to those with lower excretion (117 mmol per 24 hours). Similarly, high urinary potassium excretion (≥67 *versus* <39.4 mmol per 24 hours) was associated with a higher risk of CKD progression (HR: 1.59; 95% CI: 1.25 to 2.03).

High sodium diets have also been associated with poor CV outcomes. Hu *et al.* studied the association of urinary sodium and potassium excretion with CKD progression and all-cause mortality in 3939 CKD patients.[23] They found that higher urinary sodium excretion was associated with increased risks of CKD progression and all-cause mortality. Conversely, higher urinary potassium excretion was associated with a lower risk of CKD progression. These findings indicate that both high urinary sodium and potassium excretion are associated with an increased risk of CKD progression.

Furthermore, specific dietary factors have also been linked to CKD progression. Patients with higher consumption of low-fat milk, coffee, tea, and moderate alcohol, along with lower consumption of 100% fruit juice, whole-fat milk, artificially sweetened beverages, and sugar-sweetened beverages, were found to have a lower risk of CKD progression.[23]

Addressing metabolic acidosis through dietary modifications is another important aspect. Metabolic acidosis has been associated with CKD progression, and studies have shown that oral sodium bicarbonate supplementation can improve kidney function and slow the progression of CKD.[24, 25]

These findings emphasize the importance of adopting a healthy dietary pattern, including reduced sodium intake, increased potassium intake, and addressing metabolic acidosis, in order to mitigate the risk of CKD progression and improve kidney outcomes. Further research is warranted to explore the optimal dietary interventions for patients with CKD.

URIC ACID

In patients with CKD, uric acid (UA) levels are commonly elevated and have been traditionally associated with poor vascular and renal prognosis. Numerous studies have demonstrated that elevated serum UA levels independently predict the development of CKD.[26, 27] Animal studies have further shown that increasing UA levels can induce hypertension and renal disease, including glomerular injury and tubulointerstitial fibrosis.[60, 61] Additionally, preliminary studies in humans have suggested that reducing plasma UA concentrations may slow the progression of renal disease in individuals with CKD.

However, two recent randomized clinical trials have not improved kidney results by lowering serum UA. One of these trials is the PERL study, which involved 530 patients with type 1 diabetes mellitus and an eGFR of 40 to 99.9 mL/min/1.74 m^2 who were randomized to receive allopurinol or placebo. The study concluded that there was no clinically meaningful evidence of benefits in terms of kidney outcomes from serum urate reduction with allopurinol.[28]

The other study is the CKD-FIX trial, which included 363 CKD patients (stage 3 or 4) and randomized them to receive allopurinol or placebo. Similar to the PERL study, this trial did not find any kidney benefits associated with serum UA reduction using allopurinol. Interestingly, both studies failed to demonstrate benefits across different stages of CKD.[29]

In summary, while animal models have shown promising results, these findings have not been replicated in humans. Currently, there is a lack of evidence supporting the use of serum UA-lowering drugs for improving kidney outcomes. Further research is needed in this

field to fully understand the pathophysiology of elevated UA and its association with CKD progression.

SLEEP DURATION

Recent studies have highlighted the association between sleep disorders and various cardio-metabolic diseases. Both shorter and longer sleep duration, as well as poor sleep quality, have been identified as risk factors for cardiovascular morbidity and mortality in both healthy individuals and the CKD population. One study conducted by Ricardo *et al.*[62] investigated the association between habitual sleep duration and quality with CKD progression in 431 patients from the CRIC study. They utilized wrist actigraphy and self-reporting over 5-7 days to assess sleep duration. The findings revealed that higher sleep fragmentation, shorter sleep duration, and poor sleep quality were each independently associated with a steeper decline in eGFR and an increase in proteinuria over time.[62]

Similarly, Yamamoto *et al.* conducted a prospective cohort study involving 1601 patients from the CKD-Japan Cohort and examined the relationship between sleep duration and quality with ESKD.[63] The results showed that both shorter sleep duration (≤5 hours) and longer sleep duration (>8 hours), as well as poor sleep quality (PSQI Global Score ≥6), were associated with an increased risk of ESKD in patients with CKD.

The negative impact of sleep disorders on vascular compliance and endothelial function may also have a detrimental effect on CKD. Therefore, optimizing sleep duration and quality represents a novel target for delaying the progression of CKD. Further studies are required in this field to evaluate interventions targeting sleep disorders in the CKD population.[64]

HYPERTENSION

Arterial hypertension is highly prevalent in the CKD population, and its prevalence increases with the progression of CKD, affecting more than 90% of patients at stages 4-5 of CKD.[65] Hypertension is both a cause and an effect of kidney disease and is the second leading cause of ESKD.[66] Uncontrolled hypertension in CKD patients can significantly worsen the decrease in GFR, particularly in those with DKD.[67] In addition, hypertension in CKD is a common cause of resistant hypertension (RH), which refers to patients requiring ≥3 antihypertensive drugs, including a diuretic, to achieve blood pressure (BP) control.[30] Gorostidi *et al.* described different phenotypes using ambulatory blood pressure monitoring (ABPM) in this population, with the masked uncontrolled hypertension pattern (MUCH) being common. This pattern refers to patients with controlled office BP but uncontrolled ambulatory BP and is associated with an elevated risk of cardiovascular events.[30, 31] Moreover, CKD patients often exhibit alterations in the circadian rhythm of BP, such as non-dipping and riser dipper patterns, which are associated with increased cardiovascular risk.[68]

Combination therapy with antihypertensive drugs is frequently required to achieve BP control in this population. Targeting BP control is challenging but crucial, as it can slow the