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Review

Why Do Patients With Well-Controlled Vascular Risk Factors Develop Progressive Chronic Kidney Disease?

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ABSTRACT

Cardiovascular disease and chronic kidney disease (CKD) share several common risk factors, and CKD itself is an independent and graded risk factor for cardiovascular disease. Although control of vascular risk factors is associated with improved kidney outcomes, certain patients still show CKD progression, highlighting that examination of other factors is warranted. In this review we explore how blood pressure and glycemic targets appear to differ for macro- vs microvascular disease. Furthermore, factors such as obstructive sleep apnea and obesity are associated with CKD progression. There is increasing recognition of how sex, gender, ethnicity, and socioeconomic position all factor into CKD progression. Uncertainty exists as to what is the optimal diet to prevent loss of kidney function. Last, complications of CKD might directly or indirectly contribute to progression of kidney disease. In conclusion, control of vascular risk factors reduces the risk of CKD progression, and careful consideration of these additional factors might ultimately result in improved cardiovascular and CKD outcomes.

RÉSUMÉ

La maladie cardiovasculaire et la néphropathie chronique ont en commun plusieurs facteurs de risque. La néphropathie chronique est en soi un facteur de risque indépendant et progressif de maladie cardiovasculaire. Bien que la maîtrise des facteurs de risque vasculaire soit associée à une amélioration des paramètres rénaux, certains patients présentent quand même une évolution de la néphropathie chronique mettant en évidence la nécessité d'évaluer d'autres facteurs. Dans cette étude, nous examinons comment les valeurs cibles de la pression artérielle et de la glycémie semblent différer si l'atteinte est microvasculaire ou macrovasculaire. De plus, les facteurs comme l'apnée obstructive du sommeil et l'obésité sont liés à l'évolution de la néphropathie chronique. On reconnaît de plus en plus le rôle du sexe, du genre, de l'origine ethnique et du statut socio-économique dans l'évolution de la néphropathie chronique. L'incertitude plane quant à la diète optimale pour prévenir la détérioration de la fonction rénale. Finalement, les complications de la néphropathie chronique pourraient contribuer directement ou indirectement à l'évolution de la néphropathie. En conclusion, la maîtrise des facteurs de risque vasculaire réduit le risque d'évolution de la néphropathie chronique et la prise en considération rigoureuse de ces facteurs additionnels pourrait en fin de compte se traduire par une amélioration des issues au regard de la maladie cardiovasculaire et de la néphropathie chronique.

Chronic kidney disease (CKD) affects more than 10% of the Canadian population[1] and is considered a global epidemic.[2,3] CKD arises from a heterogeneous group of diseases that result in irreversible loss of kidney function occurring over months or years. The diagnosis of CKD is determined by chronically reduced kidney function and structural kidney damage.[4] Kidney function is determined by estimated glomerular filtration rate (eGFR) using serum creatinine[5] and is a measure of the amount of blood filtered through the functional nephrons per unit time.[5] The Canadian Society of Nephrology has endorsed the international definition of CKD as an eGFR < 60 mL/min/1.73 m^2 or markers of kidney damage, or both, for ≥ 3 months, irrespective of the underlying etiology.[6] The prognosis of kidney disease worsens as eGFR decreases and as albuminuria increases (Fig. 1).[4]

CKD and cardiovascular disease (CVD) share many risk factors, including hypertension, diabetes, smoking, dyslipidemia, obesity, and family history and there is an independent, graded association between severity of CKD and CVD risk.[7] As such, there is considerable overlap in the management of CVD and CKD because of these shared risk factors. However, despite optimal management of vascular risk factors, many patients with CVD still show CKD progression, which in turn increases CVD risk.[8-11]

Loss of kidney function is associated with, among conventional CVD risk factors, a complex interplay of kidney-related complications, including blood pressure fluctuations, dysglycemia, abnormal calcium and phosphate metabolism, acid-base

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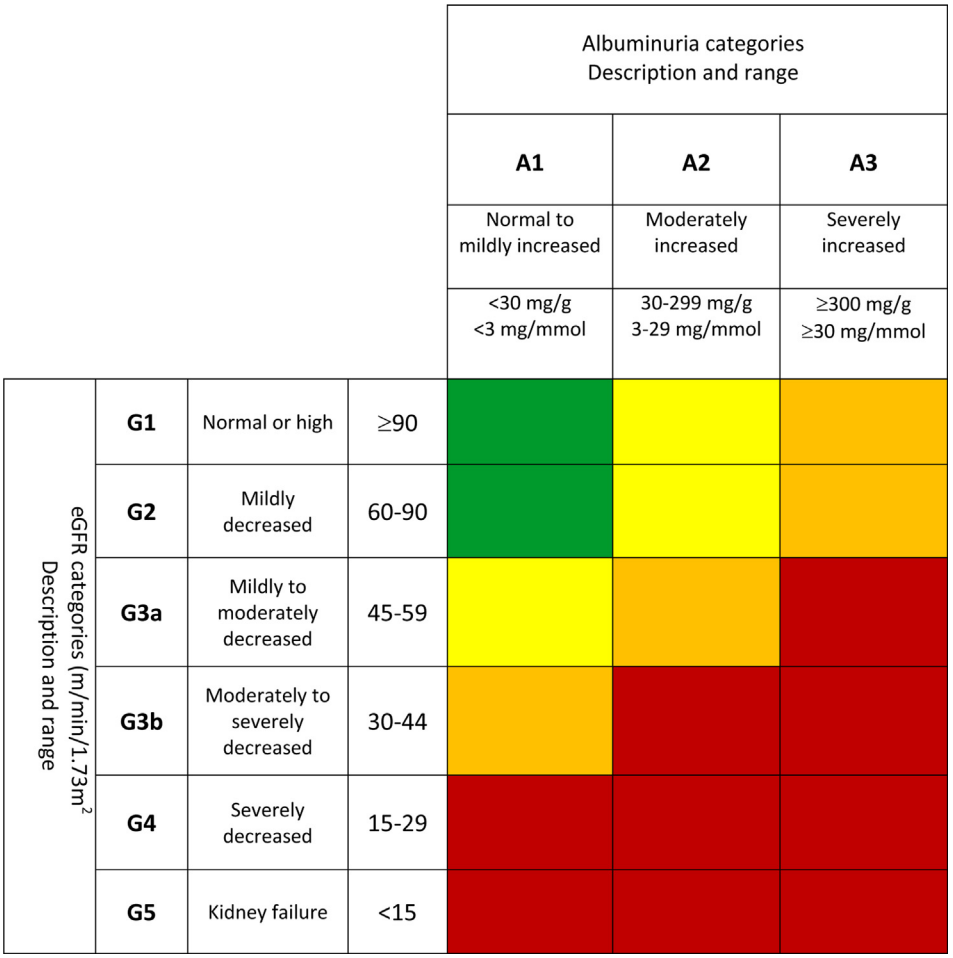

Figure 1. Prognosis of chronic kidney disease according to estimated glomerular filtration rate (eGFR) and albuminuria categories. **Green:** low risk (if no other markers of kidney disease, no chronic kidney disease); **yellow:** moderately increased risk; **orange:** high risk; **red:** very high risk. Reproduced from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group[4] with permission from Elsevier.

and electrolyte disturbances, anemia, and obstructive sleep apnea (OSA). The incidence, prevalence, and progression of CKD varies globally and even within countries, in part because of differences in ethnic background and socioeconomic position and it is likely that sex and gender also play a role. The focus of this article is to discuss why certain patients, despite careful treatment of CVD risk factors, still have CKD progression.

Aging

It is normal and expected to have loss of kidney function with increasing age. In healthy aging, significant structural changes occur in the kidney that do not result in a change in eGFR until a certain threshold is reached.[12] Total kidney volume decreases with age, but most of the decline is after the sixth[13] or seventh decade.[14] The prevalence of kidney microstructural changes increases in healthy aging, including nephrosclerosis and glomerulosclerosis, both of which have been associated with hypertension,[15,16] which in turn is associated with CKD progression.

Nephron Number

Nephron number decreases with age.[17] As an adaptive response to nephron loss, there is increased filtration per nephron leading to glomerular hypertension and subsequent glomerulosclerosis with progressive loss of kidney function. Of note, the number of nephrons present in an individual is highly variable and closely tied to birth weight,[18] with preterm infants having reduced nephron numbers at birth in proportion to gestational age.[19] Certainly, lower nephron endowment in potential kidney donors with a family history of end-stage kidney disease (ESKD) is associated with a compensatory increase in single-nephron glomerular filtration rate (GFR)[20] and larger glomeruli,[21] suggesting that even with optimization of vascular risk factors, individuals born with lower nephron mass are at increased risk of CKD progression.

Hypertension

Although hypertension is a common finding in the population with CVD and CKD, the optimal target blood pressure in patients with CKD remains unclear. A systematic review and meta-analysis of randomized controlled trials (RCTs) that compared intensive vs less intensive blood pressure-lowering treatment strategies showed an overall improvement in cardiovascular and kidney outcomes with intensive blood pressure-lowering,[22] however, the heterogeneity of the populations included limits the applicability of the

results in CKD patients.[23] As recently outlined by Ku and colleagues,[24] the lack of consistent effect of blood pressure-lowering on kidney function likely reflects the heterogeneity of mechanisms contributing to hypertension in CKD (Fig. 2). Furthermore, factors related to complications of CKD might additionally contribute to the high prevalence of hypertension in the setting of CKD. For example, patients with CKD are often anemic with significant hypoxia-induced vasodilation; the use of erythropoietin-stimulating agents and correction of anemia is associated with hypertension.[25] Secondary hyperparathyroidism results in increased intracellular calcium levels, also leading to vasoconstriction and hypertension.[26] Uremia inhibits the activity of nitric oxide synthase, further exacerbating vasoconstriction. Autoregulation normally protects the kidney from elevated systemic pressures by maintaining intraglomerular pressure; however, chronically elevated systemic arterial pressures result in impairment of glomerular autoregulation, causing glomerular hypertension, which in turn leads to nephrosclerosis and CKD progression.

How blood pressure is measured might also play a role in CKD progression. Because most trials in patients with and without CKD have used office-measured blood pressure, most guidelines refer to office blood pressure measurements when recommending treatment of hypertension in adults with CKD. However, multiple studies have shown that ambulatory blood pressure monitoring correlates more strongly with adverse kidney outcomes compared with blood pressure office measurements.[27,28]

Last, medication nonadherence is an important reason for inadequate blood pressure control.[29] Patients with CKD have amongst the highest pill burden, and nonadherence to medication is common,[30] underscoring the importance of assessing and simplifying the regimen whenever possible to minimize CVD and CKD risk.

Current Hypertension Canada guidelines[31] suggest that for patients with nondiabetic CKD the target blood pressure is $< 140/90$ mm Hg (grade B), although the guidelines acknowledge that the results of the **S**ystolic Blood **Pr**essure **In**tervention **T**rial (SPRINT)[32] might indicate that high-risk patients with nondiabetic CKD may benefit from intensive blood pressure-lowering.

The SPRINT trial included 9361 nondiabetic high cardiovascular risk participants with hypertension, 28% of whom had baseline CKD (defined as eGFR 20-60 mL/min/1.73 m^2), randomized to either an intensive (< 120 mm Hg) or standard (< 140 mm Hg) systolic blood pressure goal. The study was terminated prematurely after a median of 3.26 years, because rates of the composite cardiovascular primary outcome and all-cause mortality were reduced by 25% and 27%, respectively, in the intensively treated group. However, in participants with baseline CKD, intensive blood pressure treatment did not reduce incidence of CKD progression. Furthermore, hospitalizations or emergency room visits for acute kidney injury (AKI) occurred more frequently in the intensive compared with the standard regimen group (3.8% vs 2.3%; hazard ratio, 1.64; 95% confidence interval, 1.30-2.10; $P < 0.001$).[33] In summary, uncertainty remains on how to apply the results of the SPRINT study to the CKD population.[34]

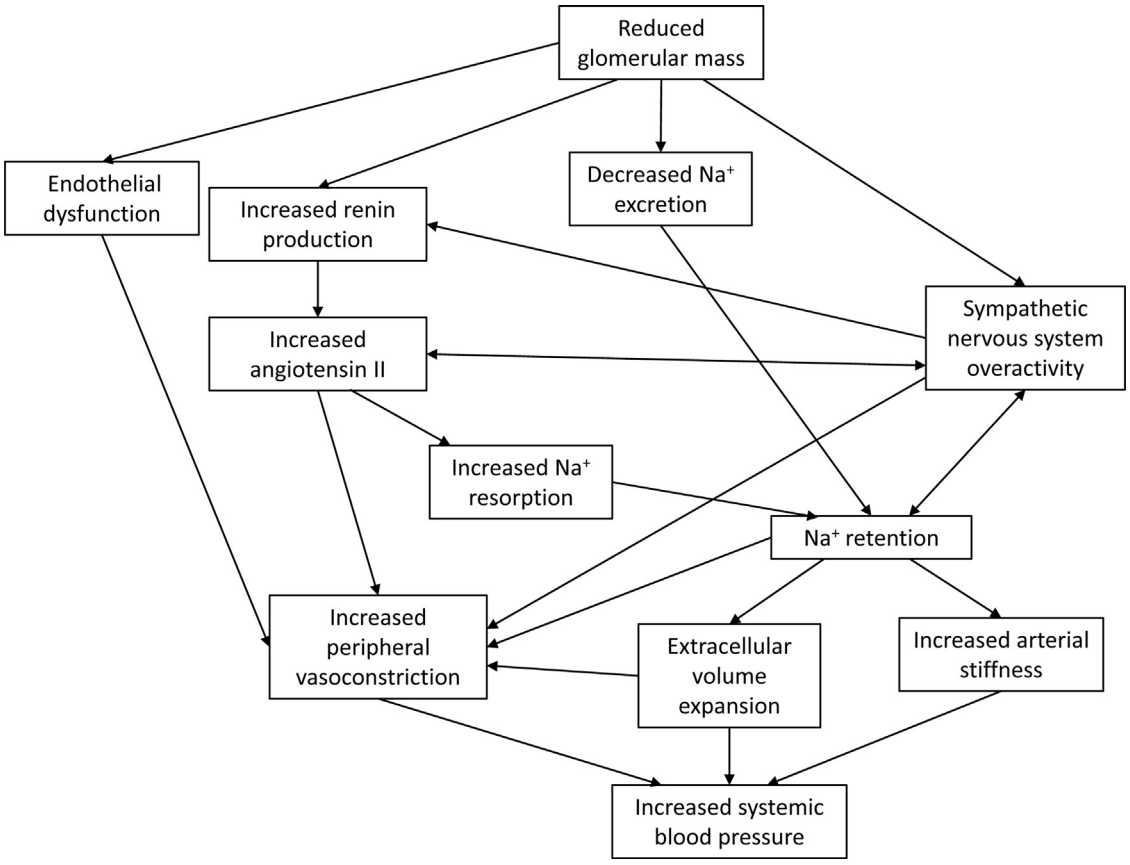

Figure 2. Mechanisms of hypertension in chronic kidney disease. Reproduced from Ku et al.[24] with permission from Elsevier.

Harmonized guidelines from Hypertension Canada and Diabetes Canada[35] do not differentiate between types 1 and 2 diabetes and state that persons with diabetes mellitus should be treated to target systolic blood pressure < 130 mm Hg (grade C) and diastolic blood pressure < 80 mm Hg (grade A). The **UK P**rospective **D**iabetes **S**tudy (UKPDS) and **Syst**olic Hypertension in **Eur**ope (Syst-Eur) trials reported a reduced risk of poor kidney outcomes with target systolic blood pressure < 150 mm Hg.[36,37] The Appropriate Blood Pressure Control in Diabetes normotensive study reported that a systolic blood pressure of < 130 mm Hg was associated with a reduced risk of albuminuria.[38] In type 1 diabetes, targeting a blood pressure of < 125/75 mm Hg was associated with a reduction in albuminuria.[39] The more recent **A**ction to **C**ontrol **C**ardi**o**vascular **R**isk in Type 2 **D**iabetes (ACCORD) Trial[40] showed that targeting systolic blood pressure < 120 mm Hg was associated with a less proteinuria progression. Of note, none of these studies showed intensive blood pressure targets improved loss of kidney function or risk of ESKD, and the ACCORD study reported more AKI events in the intensively treated group.

As recently outlined by Chang et al.,[41] intensive blood pressure-lowering on risk of ESKD is uncertain, mainly because studies have been short in duration and because acute hemodynamic effects result in a reduction in eGFR. Despite this, in patients with proteinuric CKD, a lower blood pressure goal might be appropriate. In summary, the available data suggest there might be a trade-off between kidney and CVD outcomes. As such, targeting an intensive blood pressure goal will require attention to accurate blood pressure measurement, assessing patient comorbidities and preferences, monitoring for adverse effects of treatment, and shared decision-making.[34]

Diabetes

Diabetic kidney disease (DKD) is a recognized microvascular complication and the major contributor to mortality[42-44] in types 1 and 2 diabetes mellitus and although DKD rates have remained stable at the global level since 1990, the prevalence of diabetes has increased resulting in a greater burden of DKD.[45] Approximately 40% of individuals with diabetes develop DKD and despite early detection and appropriate treatment, many patients progress to ESKD, although a post hoc analysis of patients with type 2 diabetes and microalbuminuria who underwent intensified, multifactorial treatment showed a slower loss of kidney function and a reduced risk of ESKD combined with death.[46] However, it must be noted that the patients in this study who underwent intensified treatment still had loss of kidney function and progression to ESKD, highlighting that even patients with well controlled vascular risk factors still have CKD progression. As recently outlined by Alicic and colleagues,[47] DKD risk factors can be grouped into susceptibility, initiation, and progression factors (Table 1).

Table 1. Risk factors for diabetic kidney disease

Risk factor	Susceptibility	Initiation	Progression
Demographic characteristic			
Older age	+		
Sex/gender (male/men)	+		
Race/ethnicity (black, indigenous, Hispanic, Asian/ Pacific Islander)	+		+
Hereditary			
Family history of DKD	+		
Genetic kidney disease		+	
Systemic conditions			
Hyperglycemia	+	+	+
Obesity	+	+	+
Hypertension	+		+
Kidney injuries			
AKI		+	+
Toxins		+	+
Smoking	+		+
Dietary factors			
High protein intake	+		+

AKI, acute kidney injury; DKD, diabetic kidney disease.

Reproduced from Alicic et al.[47] with permission from theAmerican Society of Nephrology.

Long-term intensive glycemic control starting early in the course of types 1 and 2 diabetes to prevent DKD is well established.[48,49] The **D**iabetes **C**ontrol and **C**omplications **T**rial (DCCT; type 1 diabetes),[48,50] and the UKPDS,[51] Kumamoto,[52] and **V**eterans **A**ffairs **D**iabetes **T**rial (VADT; type 2 diabetes)[53] trials all showed a reduction in DKD with intensive treatment aimed for a target hemoglobin A1c of approximately 7%. A reduction of CKD progression in type 2 diabetes was shown in the ACCORD trial[54,55] and the **A**ction in **D**iabetes and **Va**scular Disease: Preterax and Diamicro**n** MR **C**ontrolled **E**valuation (ADVANCE) study,[56] with target A1c values of < 6.0% and < 6.5%, respectively. However, no improvement in cardiovascular mortality or events with intensive glycemic control was observed in any of these studies and there was a high risk of hypoglycemic events in the intensively treated groups; indeed, the ACCORD study[44] was stopped early because of an increased risk of cardiovascular events with intensive treatment. Furthermore, an analysis of patients in the ACCORD study with type 2 diabetes and early-stage CKD showed 31% and 41% higher risks for all-cause mortality and cardiovascular mortality, respectively, with stringent glycemic control compared with standard therapy.[57]

The results of these studies suggest different glycated hemoglobin targets exist for micro- vs macrovascular protection. Of note, these studies did not include patients with advanced CKD who are at increased risk of hypoglycemia[58-60] and thus, the generalizability of the results of these studies to this population remains uncertain. Furthermore, the glycated hemoglobin level can be falsely low in patients with advanced CKD, particularly in the setting of an erythropoiesis-stimulating agent or intravenous iron use.[61] Diabetes Canada guidelines do not differentiate between types 1 or 2 diabetes in terms of glycemic targets for prevention of kidney disease.[62] The uncertainty of the optimal hemoglobin A1c target for prevention of CKD and progression was highlighted in a systematic review and meta-analysis of RCTs that evaluated intensive compared with less stringent glycemic control in individuals with either type 1 or 2 diabetes with and without kidney disease. People who received intensive blood glucose control had similar risks of kidney failure, major cardiovascular events, and death as people who received less intensive glycemic control, with small clinical benefits in myocardial infarction and

microalbuminuria rates. Furthermore, the potential adverse events of intensive treatment were largely unmeasured.[63] As such, Diabetes Canada clinical practice guidelines suggest that for most adults with diabetes, targeting hemoglobin A1c < 7.0% is recommended for kidney protection, although for individuals with early or no kidney disease, a lower target may be considered after balancing potential risks and benefits. Higher glycemic targets might be more appropriate for the population at risk of hypoglycemia,[62] such as those with already established CKD.

Additionally, challenges remain in terms of optimal therapeutic considerations for antihyperglycemic agents in patients with DKD.[64] As recently outlined in a systematic review and meta-analysis of RCTs and quasi-RCTs that examined comparisons of active regimens of diabetes therapy or active regimens compared with placebo/standard care in people with diabetes and CKD (eGFR < 60 mL/min/1.73 m^2), evidence concerning the safety and efficacy of diabetes therapeutic agents for people with diabetes and CKD is limited.[65] Of note, however, large RCTs have shown that sodium-glucose transport protein 2 (SGLT2) inhibitors significantly reduce the risk of important kidney outcomes, including risk of ESKD, and are effective even in individuals with advanced kidney disease.[66-68] In contrast, liraglutide use showed a 22% reduction in worsening kidney disease with the Glucagon-like peptide-1 (GLP-1) agonist vs placebo, but this result was because of a reduction in the onset of macroalbuminuria as opposed to other kidney outcomes.[69]

There is clear evidence that renin-angiotensin-aldosterone system (RAAS) blockade with either an angiotensin-converting enzyme (ACE) inhibitor[70] or an angiotensin receptor blocker (ARB)[71,72] reduces the CKD progression in the setting of diabetes. There is no role for dual blockade of the RAAS in DKD.[73] In summary, the lack of clarity in terms of target hemoglobin A1c and optimal antihyperglycemic therapeutic options likely all contribute to the potential for CKD progression in the setting of diabetes.

Obesity

Obesity, independent of associated comorbidities including diabetes and hypertension, is a risk factor for CKD progression.[74] Although the pathophysiology by which obesity results in predisposition to CKD progression is incompletely understood, glomerular hyperfiltration, increased RAAS activity, and low adiponectin levels have all been implicated.[75,76] Intensive lifestyle modifications to promote weight loss, including increased physical activity, reduce the risk of CKD, at least in the setting of diabetes.[77] However, significant effects of weight loss with medication on important kidney outcomes have not been shown to date.[75] Surgical weight loss intervention improves metabolic profile and observational studies suggest a beneficial effect on kidney outcomes,[78,79] although dedicated clinical trials are lacking.

Sex and Gender

There is increasing attention towards sex and gender differences in CKD initiation and progression. Worldwide, CKD prevalence is higher in women than in men.[80] This likely reflects sex (biological differences) and gender (socially-constructed differences) factors. An obvious sex-related factor for the higher CKD prevalence among women is that aging-associated loss of kidney function combined with women's longer life expectancy contributes to an increased population at risk of CKD.[81,82] Furthermore, the equations commonly used to estimate GFR underestimate measured GFR in women.[83,84]

Overall, population-based studies suggest that men have faster loss of kidney function compared with that in women,[85-87] although meta-analyses of studies that have examined sex differences in the setting of disease report conflicting results, which likely reflect different study populations (ie, pre- vs postmenopausal women), nature of studies included (RCTs vs observational cohorts vs CKD referrals vs population-based studies) and the outcomes assessed (slope of GFR decline vs onset of dialysis, which is influenced by gender-related factors). Preeclampsia and having a low birth weight or preterm infant are factors associated with increased risk of ESKD.[88] Endogenous and exogenous sex hormones likely play a role in CKD progression and use of oral contraceptives have been associated with diabetic nephropathy.[89] The effect of menopause on kidney function is unclear, although oral estrogen therapy has been associated with faster loss of kidney function.[90] The therapeutic benefits of treatment with ACE inhibitors and ARBs have been reported as differing between the sexes,[91] suggesting overall a higher potential ACE inhibitor/ARB effectiveness in men.[92] A discussion of sex and gender differences in CKD progression is outlined in greater detail elsewhere.[80,93,94]

Ethnicity and Socioeconomic Position

Certain racial and ethnic groups are affected disproportionately by CKD.[95-97] Canadian indigenous peoples have kidney failure rates that are two- to fourfold higher compared with the nonindigenous Canadian population.[98,99] Moreover, lower socioeconomic position, independent of other factors, is associated with worse kidney outcomes.[100-102] Furthermore, the equations to estimate GFR results in CKD might not be as accurate in non-Caucasian populations.[103,104] Potential reasons leading to racial and socioeconomic disparities in CKD progression are outlined in detail elsewhere.[105]

OSA

OSA has been discussed as a consequence of and potential risk factor for CKD.[106] OSA is more common as CKD progresses[107] and is associated with faster loss of kidney function.[108] Nocturnal hypoxemia severity is associated with increased glomerular hypertension and renal RAAS activity,[109] both of which are decreased with continuous positive airway pressure (CPAP) therapy.[110] Observational studies show inconsistent results with respect to CPAP therapy and kidney outcomes,[111] however, a recent post hoc analysis of the Sleep Apnea Cardiovascular Endpoints[112] trial showed that CPAP use in this population did not afford additional kidney protection.[113] However, the studied population were not at high risk of CKD progression and the post hoc analysis was not powered to detect a difference in eGFR decline, and so the

Table 2. Key messages: risk factors for CKD progression and potential management strategies

	Factors influencing CKD risk	Potential management strategies
BP targets	• Lower BP targets might reduce cardiovascular events and mortality but increase risk of acute kidney injury and CKD[34] • Ambulatory BP measurements correlate more strongly to kidney outcomes[27]	• Assess patient preferences and comorbidities, shared decision-making • Consider ambulatory BP monitoring in patients at high risk of CKD progression
Glycemic targets	• Intensive glycemic control in early types 1[48,50] and 2[49,51-54,56] diabetes prevents CKD • Patients with CKD are at high risk of hypoglycemia[58-60]	• Target HbA1C < 7.0% in patients with early or no CKD[62] • Patients with more comorbidities might benefit from less stringent control[62]
Obesity	• Associated with CKD progression[74] • Intensive lifestyle modifications beneficial[77]; weight loss with medication or surgical weight loss effects on CKD progression unclear[75]	• Encourage intensive lifestyle modifications
Sex and gender	• Men have faster loss of kidney function compared with women, likely because of biological and sociocultural factors[85-87] • Effect of endogenous (menses, menopause) and exogenous (contraception, postmenopausal hormone therapy) sex hormones on kidney outcomes unclear[89,90] • Pregnancy-related complications associated with CKD risk[88]	• Awareness of potential sex- and gender-related factors on kidney outcomes[80] • Interdisciplinary collaboration to provide optimal care with respect to cardiovascular, kidney and obstetrical/gynecological outcomes
Ethnicity and socioeconomic position	• Certain ethnic groups at higher risk of CKD[95-99] • Socioeconomic position inversely linked to risk of CKD progression[100,101]	• Awareness of high-risk groups that might affect follow-up plan[105] • Multidisciplinary team approach to optimize social determinants of health[105]
OSA	• OSA associated with loss of kidney function[108]; trials of OSA therapy have not included patients at high risk of CKD	• Unclear from kidney perspective; trials ongoing[114]
Diet	• Effects of salt intake on CKD progression unclear[115,116] • Dietary Approaches to Stop Hypertension diet associated with improved BP and kidney outcomes but in conflict with low protein, potassium, and phosphate kidney diet[122]	• Referral to dietitian for personalized nutrition education
Uric acid	• Elevated in CKD and associated with CKD progression[123,124]; limited data on uric acid-lowering effects[125]	• Unclear from kidney perspective
Albuminuria	• Prognostic indicator of CKD progression[127]; unclear if treatment effects on albuminuria are appropriate surrogates of CKD progression[128,129]	• Measure urinary albumin/creatinine ratio for prognostication of kidney function[4]
Acute kidney injury	• Common in hospitalized patients and increases risk of CKD[130]	• Prevention and treatment of volume depletion[134] • Avoid nephrotoxic drugs[134]
Metabolic acidosis	• Limited studies suggest correction of metabolic acidosis slows CKD progression[136]	• Consider diet rich in base-producing foods or treatment with $NaHCO_3$[137]
Volume overload	• Associated with CKD progression[138,139]	• Prevention and treatment of volume overload
Anemia	• Correction of CKD-related anemia is associated with hypertension and CKD progression[141-143]	• Iron supplementation if iron-deficient
Lack of inclusion of CKD patients in cardiovascular disease trials	• Uncertainty of risks and benefits of therapies on kidney outcomes[145]	• Dedicated cardiovascular trials in CKD populations or *a priori* prespecified subgroups of study participants with or at high risk of CKD

BP, blood pressure; CKD, chronic kidney disease; HbA1C, hemoglobin A1C; OSA, obstructive sleep apnea.

possibility remains that a higher CKD risk population might derive benefit from OSA treatment.[114]

Dietary Prevention of CKD

Current Hypertension Canada guidelines[31] suggest a low-salt diet for prevention of hypertension. However, a quantitative review showed no robust evidence suggesting that long-term reduction of salt intake results in CKD prevention or delays CKD progression.[115] However, most included studies with people with only mild kidney impairment, and thus how generalizable the results are to patients with more advanced CKD is unknown. High and low sodium intakes are associated with increased risk for CKD in hypertensive individuals with normal kidney function.[116] As kidney function declines, phosphorus homeostasis becomes dysregulated and serum phosphate levels increase. Increased dietary phosphorus has been reported to initiate and worsen CKD progression.[117] Increased serum phosphorus levels have been associated with CKD progression,[118-121] although this is not a universal finding.[121] The Dietary Approaches to Stop Hypertension (DASH) diet is recommended to hypertensive and normotensive individuals at risk of developing hypertension,[31] and this diet is also associated with decreased risk of incident CKD.[122] Although the DASH diet contains a higher protein, potassium, and phosphorus content than recommended for patients with CKD stages 3-4, ingesting a DASH-style diet was independently associated with lower risk for CKD.[122] As such, the optimal diet for prevention of CKD progression is unclear.

Uric Acid

Serum uric acid is commonly elevated in CKD patients, and reports suggesting an association between hypuricemia and CKD progression have renewed interest in this potential risk factor.[123] A small unblinded single-centre randomized trial of 113 patients reported slower CKD progression in patients treated with allopurinol compared with standard therapy, an effect that persisted 5 years post trial.[124] A systematic review that examined the effects of uric acid-lowering therapy on kidney outcomes highlighted there is limited data from low-quality studies suggesting that decreasing uric acid might prevent CKD progression.[125]

Proteinuria

Proteinuria, and specifically albuminuria, is a major prognostic indicator of kidney damage and CKD progression.[126] The Steno hypothesis suggests that albuminuria is a marker of subclinical kidney disease and represents systemic endothelial dysfunction.[127] A 2018 meta-analysis of blood pressure-lowering therapies suggested that drug effects on proteinuria or albuminuria were not good surrogates for ESKD.[128] However, a subsequent systematic review and meta-analysis that did not restrict according to intervention type reported that the treatment effect on proteinuria or albuminuria were consistent with treatment effect on ESKD.[129]

AKI

AKI is a diverse group of conditions characterized by an abrupt decrease in kidney function occurring over a maximum of 7 days.[130] AKI is estimated to occur in 20-200 per million in the community population, 7%-18% of hospitalized patients, and approximately 50% of intensive care unit patients.[131,132] AKI survivors are at increased risk of developing CKD.[133] Broad measures to reduce risk include prevention and treatment of volume depletion and avoidance of nephrotoxic drugs and are discussed in greater detail elsewhere.[134] Risk prediction equations exist as to which patients will develop CKD post AKI.[135]

Metabolic Acidosis

The prevalence of metabolic acidosis in CKD, defined as serum bicarbonate levels < 22 mmol/L, increases as GFR declines (typically to < 30 mL/min/1.73 m^2) and has been associated with CKD progression. Limited studies have suggested that correction of metabolic acidosis with oral alkali slows loss of kidney function. A systematic review and meta-analysis consisting of 7 RCTs (815 patients) receiving oral alkali therapy and its effects on kidney function reported a net GFR improvement of 3.1 mL/min/1.73 m^2, 95% confidence interval, 1.3-4.9) at end of follow-up (3 months to 5 years) compared with the non-bicarbonate therapy group.[136] In an RCT of 108 patients with stage 3 CKD treated with ACE inhibitors, a diet rich in base-producing fruits and vegetables yielded similar benefits compared with sodium bicarbonate in terms of preservation of kidney function over a 3-year period.[137]

Volume Overload

A prospective cohort of patients with stages 3-5 CKD reported that volume overload was independently associated with a greater risk of ESKD or a 50% increase in serum creatinine.[138] Moreover, patients with volume-dependent hypertension were at greater risk than those with non−volume-dependent hypertension.[138] A more recent study reported that volume overload among patients with CKD and hypertension was common and that CKD patients with uncontrolled hypertension were more likely to be volume-expanded with increased arterial stiffness, a risk factor for adverse cardiorenal outcomes.[139]

Anemia

Erythropoietin (EPO) deficiency is the most common cause of anemia in CKD, and erythropoiesis-stimulating agents have been proposed to protect kidney tissues directly via activation of EPO receptors on kidney cells resulting in decreased cell apoptosis, or indirectly through improved oxygen delivery as result of increased numbers of hemoglobin-containing red blood cells.[140] However, multiple systematic reviews do not support a role for clinical renoprotection by erythropoiesis-stimulating agents,[141-144] and targeting higher hemoglobin levels in CKD elevates risks for numerous adverse outcomes, including ESKD.

Summary

Although there are many common factors that contribute to CVD and CKD, CKD progression might still occur because of uncertainty regarding optimal blood pressure and glycemic targets, and of the role of sex, gender, and ethnicity differences, OSA, and contributions of CKD-specific factors (Table 2). Consideration as to how these factors might contribute to CKD progression as well as greater inclusion of CKD patients in CVD trials[145] are warranted, with the ultimate goal of improving CVD and CKD outcomes.

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