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CKJ Review

CKJ REVIEW

Management of traditional risk factors for the development and progression of chronic kidney disease

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ABSTRACT

Chronic kidney disease (CKD) and its downstream complications (i.e. cardiovascular) are a major source of morbidity worldwide. Additionally, deaths due to CKD or CKD-attributable cardiovascular disease account for a sizeable proportion of global mortality. However, the advent of new pharmacotherapies, diagnostic tools, and global initiatives are directing greater attention to kidney health in the public health agenda, including the implementation of effective strategies that (i) prevent kidney disease, (ii) provide early CKD detection, and (iii) ameliorate CKD progression and its related complications. In this Review, we discuss major risk factors for incident CKD and CKD progression categorized across cardiovascular (i.e. hypertension, dyslipidemia, cardiorenal syndrome), endocrine (i.e. diabetes mellitus, hypothyroidism, testosterone), lifestyle (i.e. obesity, dietary factors, smoking), and genetic/environmental (i.e. CKDu/Mesoamerican nephropathy, APOL1, herbal nephropathy) domains, as well as scope, mechanistic underpinnings, and management.

LAY SUMMARY

In this Review, we discuss major risk factors for incident chronic kidney disease (CKD) and CKD progression categorized across cardiovascular (i.e. hypertension, dyslipidaemia, cardiorenal syndrome), endocrine (i.e. diabetes mellitus, hypothyroidism, testosterone), lifestyle (i.e. obesity, dietary factors, smoking), and genetic/environmental (i.e. CKDu/Mesoamerican nephropathy, APOL1, herbal nephropathy) domains, as well as scope, mechanistic underpinnings, and management.

Keywords: chronic kidney disease, risk factors, traditional

INTRODUCTION

The global prevalence of chronic kidney disease (CKD) is approximately 9.1%–13.4% [1, 2], and is a major source of morbidity and mortality. As the twelfth leading cause of worldwide mortality, deaths due to CKD or due to CKD-attributable cardiovascular disease are estimated at 1.2 million and 1.4 million, respectively [1, 3]. International data show that, while the age-standardized mortality for other chronic diseases (i.e. cardiovascular disease, cancer, chronic obstructive pulmonary disease)

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has declined over the past two decades, a similar reduction in age-standardized deaths has not been observed for CKD [1].

Given the ill effects of CKD on health and survival [4], there is compelling need to (i) identify populations at risk of and in early stages of kidney disease, and (ii) improve access to evidence-based treatments that retard or halt kidney disease progression. Globally, executive orders such as the US Advancing American Kidney Health Initiative have sought to stimulate greater attention to kidney health in the public health agenda [5]. Additionally, the advent of new pharmacotherapies and diagnostic tools have catalysed a renewed focus on targeting key contributors to CKD. In this Review, we summarize the major risk factors for the development of incident CKD and CKD progression, categorized across cardiovascular, endocrine, lifestyle, and genetic/environmental domains. Focusing on their most common traditional CKD risk factors, we discuss their prevalence, mechanistic underpinnings, and management (Table 1).

RISK FACTORS FOR CHRONIC KIDNEY DISEASE

Cardiovascular

Hypertension

Hypertension is estimated to affect approximately 1.39 billion people (31.1%) worldwide, and it is closely linked to CKD [6]. In the USA, CKD was found to be present in about 15% of all hypertensive patients, while hypertension was comorbid in about 90% of the Medicare CKD population [7, 8]. In terms of underlying pathophysiology, chronically elevated systemic blood pressure results in remodelling of the afferent arteriole, hampering its ability to autoregulate intraglomerular pressure. Subsequently, elevated systemic pressures are directly transmitted to the vascular beds resulting in glomerular hypertension and progressive nephrosclerosis [9].

Accurate blood pressure readings are critical to hypertension diagnosis and management. Major clinical trials rely on at least two serial in-office blood pressure measurements: avoidance of caffeine and exercise 30 minutes before, quiet rest 5 minutes before, sitting down with feet flat to the ground and back support, and placing the cuff arm at the level of the atrium [9–11]. However, the CKD population has shown a tendency towards blood pressure variability outside the detection of in-office measurements, such as masked hypertension or nocturnal hypotension [12]. These entities are often underdiagnosed and underappreciated in specific subpopulations, with the Jackson Heart Study showing a prevalence of masked hypertension in more than half of its black participants (52.2%) and another study in CKD patients showing a prevalence of 27.8% [13, 14]. Multiple studies have shown that cardiovascular risk is more accurately predicted by home blood pressure monitoring and 24-hour ambulatory blood pressure monitoring compared to in-office measurements [15, 16]. However, it is notable that no large clinical trial completed thus far has used 24-hour ambulatory blood pressure monitoring to guide therapy for hypertension, and thus targets based on ambulatory blood pressure are not strictly evidence based.

Blood pressure target recommendations currently differ across various organizational guidelines. Recently, the Kidney Disease Improving Global Outcomes (KDIGO) 2021 guidelines recommended targeting a systolic blood pressure (SBP) goal of less than 120 mmHg in CKD patients, although placing a heavy emphasis on individualizing goals based on patient characteristics and tolerance of intensive blood pressure therapy [17]. On the other hand, the 2017 American College of Cardiology and American Heart Association Hypertension (ACC/AHA) guidelines target a goal of blood pressure ≤130/80 mmHg in CKD patients, while the European Society of Hypertension-European Society of Cardiology committee recommends a goal blood pressure of less than 140/90.

The rationale behind the targets recommended by these various organizations largely rests on five randomized clinical trials comparing intensive vs. standard blood pressure control regimens [11, 18–21], summarized in Table 2. Briefly, earlier trials that examined blood pressure targets in CKD patients alone found that intensive control only provided benefit at reducing the rate of eGFR decline in patients with baseline proteinuria >1 g/day. These trials did not detect differences in mortality nor cardiovascular protection but were underpowered to detect these outcomes [18–20]. The Action to Control Cardiovascular Risk in Diabetes (ACCORD-BP) trial was a subsequent larger trial examining primarily cardiovascular outcomes based on differing blood pressure targets in diabetic patients but had strict exclusion criteria to remove CKD patients from their study population [21]. It was not until the 2015 Systolic Blood Pressure Intervention Trial (SPRINT), a large randomized clinical trial of 9361 patients, where the cardiovascular benefits of intensive blood pressure reduction were more clearly shown [11]. Despite not analysing renal outcomes as their primary outcome, a *post hoc* analysis examining the substantial CKD subcohort of 2646 patients in the SPRINT trial still showed significant reductions in cardiovascular outcomes and overall mortality with the lower blood pressure goal of SBP <120 mmHg but did not find differences in renal outcomes [22]. These findings of cardiovascular and mortality benefit with stricter blood pressure control in the CKD population continue to be supported by meta-analyses of these clinical trials [23, 24].

Non-pharmacologic interventions to reduce blood pressure in CKD patients should be attempted first or used in conjunction with pharmacologic therapies. Current guidelines still recommend a low salt diet, targeting <2 g per day [17]. Studies have correlated higher urinary sodium excretion to both worse renal and cardiovascular outcomes [25, 26], and reduced dietary sodium intake can cause reductions in proteinuria by 22% [27]. Of note, a recent clinical trial comparing the use of salt substitutes (25% potassium chloride) compared to regular salt (100% sodium chloride) found decreased rates of stroke, major adverse cardiovascular events, and death [28]. Whereas this study found no impact on safety events related to hyperkalaemia in the general population, a modelling study did report an increase in mortality attributable to hyperkalaemia from salt substitutes in the CKD population albeit with an overall net reduction in mortality when compared to its cardiovascular benefits [29].

Other lifestyle interventions impacting hypertension in CKD patients include moderate-intensity exercise for at least 150 minutes per week, treatment of sleep apnoea, weight loss, and avoiding nonsteroidal anti-inflammatory pain medications. More recently, trials have demonstrated the potential utility of renal denervation, or radiofrequency ablation of nerves around the renal artery, to treat refractory or resistant hypertension [30]. A small study explored renal denervation in stages 3–4 CKD patients with about 30 mmHg reduction in SBPs and significant decreases in nocturnal ambulatory blood pressures as well [31]. Larger trials will be needed before this procedure can be recommended in CKD hypertension guidelines.

In terms of pharmacologic therapies, the renin-angiotensin-aldosterone system (RAAS) inhibitors such as angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor

Table 1: Prevalence, mechanisms, and management of risk factors for the development and progression of CKD.

Risk factor	Prevalence	Mechanisms	Management
Endocrine			
Diabetes Mellitus	25%–40%[a] [143]	Glomerular hyperfiltration Overactivation of RAAS Oxidative stress Immune dysfunction	Individualized HgbA1c targets <6.5%–8.0% RAAS blockade GLP-1 receptor analogues SGLT-2 inhibitors
Hypothyroidism	55.5%[b]	Decreased cardiac output Decreased RAAS activity Altered renal haemodynamics Increased tubuloglomerular feedback	Levothyroxine replacement
Testosterone	Further research needed	Oxidative stress Fas-FasL mediated apoptosis Excessive extracellular matrix deposition Hypertension	Further research needed
Cardiovascular			
Hypertension	15%–30%[a] [7, 143]	Remodelling of afferent arteriole → direct transmission of blood pressure → progressive nephrosclerosis	Lifestyle modifications - Low salt diet - Exercise - Weight loss ACEi/ARB - First line in proteinuric CKD Diuretics CCBs MRAs SGLT-2 inhibitors
Dyslipidaemia	53.9%[b]	Lipid accumulation → oxidative stress, lipid peroxidation and mitochondrial damage	Lifestyle modifications Statin therapy for eGFR <60 ml/min/1.73 m^2 indicated if: - Age ≥50 years old, or - Age 18–49 and one of the following: ◦ Coronary artery disease ◦ Diabetes mellitus ◦ Prior ischaemic stroke ◦ 10-year risk of coronary death or myocardial infarction >10%
Cardiorenal	49%–91%[a] [60, 61]	Reduced cardiac output → reduced renal perfusion → renal ischaemia Increased central venous and intra-abdominal pressures → renal venous congestion Oxidative stress Inflammatory mediators	Symptomatic Management - Loop diuretics ± Metolazone Survival Management - β-blockers - ACEi/ARBs - MRAs - Ivabradine - Angiotensin receptor neprilysin inhibitors - SGLT-2 inhibitors - Device therapies
Lifestyle			
Obesity	17%[a] [143]	Altered renal haemodynamics Inflammation Oxidative stress	Weight loss, esp. bariatric surgery GLP-1 receptor agonists RAAS blockade
Dietary Factors	Further research needed	Dietary acid load Uremic toxins by gut microbiota Cardiovascular comorbidities	Plant-based low protein (PLADO) diet intake ↓ saturated fat intake, ↑ mono and unsaturated fat intake ↓ sodium intake
Smoking	50%[b]	Oxidative stress	Smoking cessation
Environmental			
CKDu	9%–18%[b]	Intense heat & strenuous working conditions → dehydration → pre-renal injury	Hydration
APOL1	20%[b]	Podocyte cytotoxic injury	Avoid preventable infections
Herbal Nephropathy	50%[b]	Interstitial fibrosis	Avoid offending agents

[a]Prevalence of CKD in risk factor population.
[b]Prevalence of risk factor in CKD population.
Abbreviations: RAAS, renin-angiotensin-aldosterone system; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2; CKD, chronic kidney disease; ACEi, angiotensin-converting enzyme inhibitor; ARB, aldosterone receptor blocker.

Table 2: Randomized clinical trials comparing intensive vs. standard blood pressure control regimens in CKD patients.

			BP goal		CKD population		Results		
Trial	Year	Primary outcome	Standard	Intensive	Key characteristics	Size	Mortality	CV protection	Renal protection
MDRD	1995	Rate of eGFR change; change in proteinuria	MAP $\leq$ 107 mmHg	MAP $\leq$ 92 mmHg	eGFR 15–55 ml/min/ 1.73 m^2	840	n/a	n/a	Decreased eGFR decline in intensive BP control group if baseline proteinuria >1 g/day
AASK	2002	Rate of eGFR change; composite 50% reduced GFR, ESRD, or death	MAP 102–107 mmHg	MAP $\leq$ 97 mmHg	eGFR 20–65 ml/min/ 1.73 m^2 African-American Non-diabetic	1094	No difference (not powered)	No difference (not powered)	Decreased eGFR decline in intensive BP control group if baseline proteinuria >1 g/day
REIN-2	2005	Time to ESRD	DBP < 90 mmHg	BP < 130/80 mmHg	eGFR <70 ml/min/ 1.73 m^2 Proteinuria > 1 g/day Non-diabetic On ACEi	335	No difference (not powered)	No difference (not powered)	No difference in time to ESRD
ACCORD	2010	Composite of MI, stroke, or CV death	SBP < 140 mmHg	SBP < 120 mmHg	Type 2 diabetics Creatinine $\leq$ 1.5 mg/dl Proteinuria < 1 g/day	n/a	No difference	Decreased stroke risk in intensive BP control group	n/a
SPRINT	2015	Composite of MI, other ACS, stroke, HF, or CV death	SBP < 140 mmHg	SBP < 120 mmHg	eGFR >20 ml/min/ 1.73 m^2 Non-diabetic	2646	Decreased in CKD cohort in intensive BP control group	Decreased primary outcome in CKD cohort in intensive BP control group	No difference in renal outcomes

Abbreviations: MDRD, Modification of Diet in Renal Disease; AASK, African-American Study of Kidney Disease and Hypertension; REIN-2, blood pressure control for renoprotection in patient with non-diabetic chronic renal disease; MAP, mean arterial pressure; DBP, diastolic blood pressure, BP, blood pressure; CV, cardiovascular.

blockers (ARB) are considered first line for patients with hypertension and proteinuric CKD [17, 32]. Studies have demonstrated their ability to reduce the risk for developing CKD progression and cardiovascular morbidities by about 50% [33]. Even in patients reaching stages 4-5 CKD, a recent trial found that continuing ACEi/ARB therapy was associated with decreased mortality and major cardiovascular events, albeit with an increased risk of initiated kidney replacement therapy [34]. In non-proteinuric CKD, the evidence is less clear regarding the superiority of RAAS inhibitors compared to other anti-hypertensives. Combinations of ACEi with an ARB or direct renin inhibitor are not recommended. Serum creatinine may be expected to rise to 30% within the first 4 weeks of starting RAAS blockade, but should be discontinued for increases of >30% [17].

Mineralocorticoid receptor antagonists (MRAs) such as spironolactone and eplerenone have been shown to reduce proteinuria as well [35] but should be closely monitored for hyperkalaemia in CKD patients with eGFR <45 ml/min/1.73 m^2 [17]. Finerenone, in particular, a nonsteroidal and selective MRA, has recently been shown to reduce CKD progression and cardiovascular events in patients with comorbid CKD and type 2 diabetes [36, 37]. Cardiovascular outcomes were shown to be improved even in stages 1-2 CKD patients with severely elevated albuminuria [38].

Diuretics are another important tool to help reduce the volume overload seen in CKD patients. Thiazides such as chlorthalidone are initially preferred due to their long half-life [32], with recent clinical trial data showing improvement in blood pressure at advanced stages of CKD (i.e. stage 4 CKD) [39]. While loop diuretics such as furosemide remain effective for diuresis at lower GFRs relative to thiazides, benefit on clinical outcomes have not yet been demonstrated [17]. Sodium-glucose cotransporter 2 (SGLT-2) inhibitors, which also have both diuretic and antihypertensive effects, can decrease blood pressure by about 7–9 mmHg, although not all the renal and cardiovascular benefits can be explained by blood pressure reduction alone [40–43].

Both non-dihydropyridine (i.e. verapamil, diltiazem) and dihydropyridine (i.e. amlodipine, felodipine) calcium channel blockers (CCBs) have been shown to be efficacious in reducing proteinuria in CKD patients when used in conjunction with RAAS blockade [44, 45]. The combination of benazepril with amlodipine in particular was shown to be more effective than the combination with hydrochlorothiazide in the Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial at preventing the doubling of serum creatinine and end-stage renal disease (ESRD) [45].

Other agents such as β-blockers, α-blockers, and direct vasodilators like minoxidil and hydralazine have not been shown to have significant renoprotective effects and should not be used before the aforementioned agents have been exhausted [46]. However, in clinical practice, it is common to encounter the use of later line agents in advanced CKD patients due to the side-effect profile of the aforementioned agents such as hyponatraemia (i.e. thiazides), hyperkalaemia (i.e. ACEi/ARB, MRAs), and oedema (i.e. CCBs).

Dyslipidaemia

Patients with dyslipidaemia show heightened risk of developing CKD. One recent study of 5183 patients in China during a 6-year follow-up period showed that in the highest quartiles of low-density lipoprotein (LDL), triglycerides, and total cholesterol, the risk of developing incident CKD increased by 1.4-, 3.1-, and 3.8-fold, respectively [47]. While another Japanese study showed that hypercholesterolaemia, hypertriglyceridaemia, and low high-density lipoprotein (HDL) levels were all independently associated with worsening proteinuria in a 10-year follow-up study, the overall literature suggests the association with progression of CKD is still controversial [48, 49]. Another important regulator of lipid homeostasis, proprotein convertase subtilisin/kexin type 9 (PCSK9), was recently shown to be associated with increased risk of cardiovascular disease in a CKD population, but had no relation with eGFR or albuminuria [50]. In terms of pathophysiology, the dyslipidaemia associated with CKD seems to primarily be comprised of high triglyceride levels, low HDL levels, and variable LDL levels [51, 52]. Excess lipid accumulation causes damage to podocytes, tubular cells, and tubulointerstitial tissue by various mechanisms including production of reactive oxygen species, lipid peroxidation, and mitochondrial damage leading to glomerular and tubular lesions [51].

Guidelines for initiating and monitoring statin therapy by the United States Preventive Services Task Force and the ACC/AHA currently do not comment specifically on individuals with CKD. The atherosclerotic cardiovascular (ASCVD) risk calculator also does not include CKD status [32, 53]. KDIGO guidelines recommend measuring a lipid profile for newly diagnosed CKD and starting statin or statin-ezetimibe combination therapy in adults aged ≥50 years old with eGFR <60 ml/min/1.73 m^2. For adults aged 18–49 with CKD, the guidelines recommend statin therapy if there is also one of the following comorbidities: known coronary disease, diabetes mellitus, previous ischaemic stroke, or 10-year risk of coronary death or non-fatal myocardial infarction >10% [54]. Studies have demonstrated cardiovascular benefits for starting statin therapy in the CKD population, with reduction of major cardiovascular events by 23%–28% [55]. However, this reduction becomes relatively smaller as eGFR declines [56] and no major trials thus far have demonstrated any benefit of statin therapy for preventing or ameliorating adverse renal outcomes [57–59]. Other pharmaceuticals besides statin therapy including niacin, fibrates, fish oil, bile acid resins, and (PCSK9 inhibitors have not been well studied in the CKD population, although there is emerging interest in niacin for its phosphorus-lowering effects [52].

Cardiorenal syndrome

The cardiorenal syndrome, a term used to describe the synchronous dysfunction of the heart and kidneys by complex feedback mechanisms, also contributes significantly to the CKD population. One meta-analysis estimates CKD (eGFR <60 ml/min/1.73 m^2) to be prevalent in about half (49%) of the total heart failure population, with higher prevalence in the acute heart failure (53%) compared to chronic heart failure (42%) [60]. In another database, the Acute Decompensated Heart Failure National Registry (ADHERE), 91% of the more than 105 000 participants had some degree of renal dysfunction (eGFR <90 ml/min/1.73 m^2) [61]. Heart failure patients with CKD also portend a greater than 2-fold higher mortality risk compared to their non-CKD counterparts [60].

Management of heart failure patients focus on both symptoms and overall survival. Diuretic therapies with loop diuretics are often required at higher doses and/or used in combination with metolazone in patient with lower GFRs to help improve shortness of breath and peripheral oedema. While thiazide diuretics were previously thought to be ineffective in stages 4–5 CKD [62], a recent clinical trial has shown efficacy

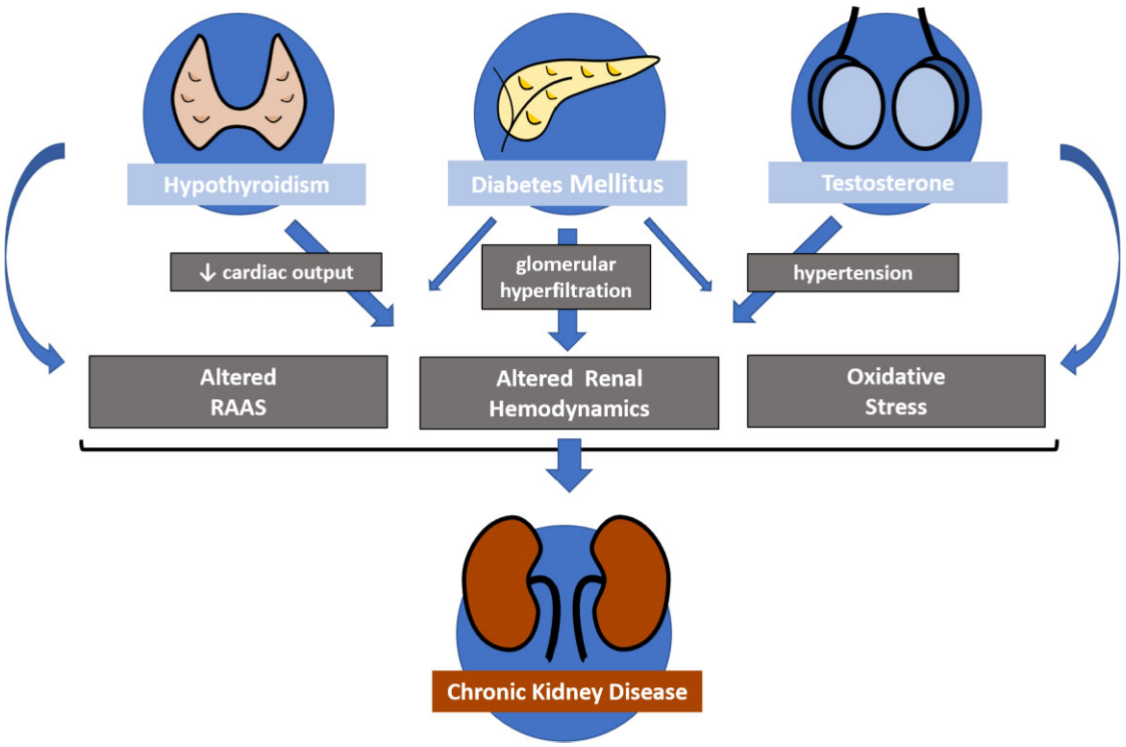

Figure 1: Conceptual figure of endocrine risk factors of CKD.

of chlorthalidone in improving blood pressure among advanced CKD patients with poorly controlled hypertension [39]. Notably, most heart failure clinical trials have excluded patients with eGFR <30 ml/min/1.73 m^2. However, trials have demonstrated survival benefit in patients with both heart failure with reduced ejection fraction and stages 1–3 CKD for β-blockers [63], ACEi/ARBs [64], and MRAs [65]. Other newer medications have also demonstrated benefit. Ivabradine and angiotensin receptor neprilysin inhibitors both demonstrated improved cardiac death and heart failure hospitalization outcomes in trials with CKD patients [66, 67]. SGLT-2 inhibitors in particular have shown significant promise with trials demonstrating not only reductions in cardiovascular death and heart failure hospitalizations by 25%, but also 50% reduction in the incidence of kidney replacement therapy or sustained loss of eGFR [68]. Device therapies for heart failure with reduced ejection fraction, such as cardiac resynchronization therapy and internal cardioverter and defibrillators, have demonstrated similar benefit in stage 3 CKD patients compared to those with eGFR >60 ml/min/1.73 m^2 [69, 70]. Given the high cardiovascular mortality of CKD patients, further investigation of the risks and benefits of permissive hypercreatininaemia in the context of interventions that optimize heart failure status are needed.

Endocrine

Diabetes mellitus

There are various endocrine risk factors for CKD, including diabetes mellitus (Fig. 1) [71]. Of the estimated 374 million individuals with diabetes worldwide [72], about one-half of type 2 diabetics and one-third of type 1 diabetics will develop CKD [73]. One study found that CKD due to diabetes resulted in 11 million disability-adjusted life years (DALYs), the largest contribution to CKD DALY burden of any cause and the only cause to show a significant increase in DALY rate from 1990 to 2017 [1]. The pathophysiological mechanisms of diabetic kidney disease include glomerular hyperfiltration from overactivation of the RAAS system, oxidative stress, and immune dysfunction leading to mesangial expansion and glomerular filtration barrier damage [74].

Cornerstones of CKD management in diabetic patients include strict glycaemic control to prevent CKD onset and early progression, and RAAS blockade, glucagon-like peptide-1 (GLP-1) receptor analogues, SGLT-2 inhibitors to prevent progression of overt CKD. Multiple trials have demonstrated decreased rates of CKD with lower HgbA1c targets, including a 22-year follow-up of the Diabetes Control and Complications (DCCT) trial that showed 50% reduction of CKD incidence in the intensive glucose control group [75, 76]. However, other trials involving type 2 diabetes failed to demonstrate improved kidney outcomes with stricter control of HgbA1c and instead showed increased mortality and risk of hypoglycaemia [10, 77]. Thus, current guidelines recommend selecting an individualized goal from a broader range of HgbA1c values, <6.5%–8.0%, balancing the benefits of renal and cardiovascular protection with the risks of hypoglycaemia [78].

Trials examining the effect of ACEis and ARBs on type 2 diabetics have shown a reduction in composite endpoint of doubling of serum creatinine, death, and kidney failure by 16%–20% over three years, independent of blood pressure reduction [79]. As mentioned in the hypertension section, recent trials regarding finerenone in type 2 diabetic patients have also shown a 17.8% decrease in CKD progression events and a 14.8% decrease in cardiovascular events [36]. GLP-1 receptor analogue trials have shown more than 25% decreased risk of stage A3 kidney disease (>300 mg urine albumin/g urine creatinine) over 3.8 years in type 2 diabetic patients, alongside their cardiovascular

protective effects [80–82]. Last, SGLT-2 inhibitor trials have shown considerable promise in reducing cardiovascular outcomes as well as diabetic kidney disease progression [83, 84]. Recent trials powered for renal outcomes such as the Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE) trial showed reduction by 30% of a composite outcome of doubling of serum creatinine, renal or cardiovascular death, and kidney failure in the canagliflozin arm [85]. The Dapagliflozin in Patient with Chronic Kidney Disease (DAPA-CKD) trial interestingly showed a similar reduction not only in type 2 diabetics but also for non-diabetic kidney disease, further highlighting the significance of this class of medications in preventing progression of CKD [86].

Hypothyroidism

Hypothyroidism is highly prevalent in kidney disease, with various large population-based studies showing approximately 25% of patients with moderate-to-advanced CKD affected by this endocrine disorder [87–89]. Studies have also confirmed a higher prevalence of hypothyroidism with increasing severity of kidney function. Those with eGFR <30 ml/min/1.73 m^2 were twice as likely to have hypothyroidism as those with eGFR >60 ml/min/1.73 m^2 [87], and each decrement of 10 ml/min/1.73 m^2 of eGFR was associated with an 18% higher risk of hypothyroidism and 0.11 mIU/l higher serum TSH level [89]. The precise mechanisms linking thyroid and kidney disease are still unknown. However, several potential mechanisms have been identified, including decreased cardiac output, altered intrarenal haemodynamics, reduced RAAS production and activity, and increased tubulo-glomerular feedback due to changes in chloride channel and expression [88].

Whereas there is overall limited literature regarding the effects of levothyroxine replacement in hypothyroid CKD patients, studies have noted decreased renal disease progression in CKD patients treated for subclinical hypothyroidism [90, 91], as well as decreased mortality in those with ESRD [92, 93]. A small randomized trial of 136 patients with subclinical hypothyroidism and early type 2 diabetic nephropathy showed decreased urinary albumin excretion and LDL cholesterol when treated with 48 weeks of levothyroxine versus placebo [94]. Although the TSH target recommendations specifically for the CKD population have not yet been established, one study demonstrated that incrementally higher TSH levels (comparing >5.0 mIU/l with >10.0 mIU/L) in CKD patients were associated with higher post-ESRD mortality [92]. Given levothyroxine's narrow therapeutic window and potential to cause complications such as arrhythmia, reduced bone mineral density, and increased protein catabolism in the non-CKD population, larger trials are needed to ensure the safety and efficacy of thyroid hormone supplementation in CKD patients.

Testosterone

Males have a higher incidence of CKD and faster progression of kidney disease when compared to females [95]. Currently, there are a lack of well-established explanations for this sex discrepancy. However, sex hormones have been suggested as a possible contributing cause. The glomerular extracellular matrix is controlled by mesangial cells and is stimulated by transforming growth factor-β (TGF-β) [96]. In animal studies, TGF-β expression is increased by testosterone and decreased by oestradiol, and excessive expression of TGF-β can lead to glomerulosclerosis-mediated kidney disease from excessive extracellular matrix deposition [96]. In addition, testosterone is associated with increased reactive oxygen species (ROS) mediated renal injury, either by directly inhibiting antioxidant enzymes or indirectly magnifying ROS production during acute renal injury. In contrast, oestrogen inhibits the production of ROS during acute renal injury [97]. Testosterone can also directly induce renal tubule cell injury by activating the Fas-FasL mediated apoptosis pathway, which is inhibited when oestradiol is present [98]. Finally, testosterone is associated with hypertension through hypothesized RAAS stimulation, increased renal sodium reabsorption, and/or increased vascular resistance from amplified vascular smooth muscle cell proliferation. These mechanisms ultimately result in hypertension-mediated renal injury [99].

Lifestyle

Obesity

Obesity has been described by multiple epidemiological studies to be independently associated with CKD. In one study, an increase in weight of >10% of the baseline BMI resulted in an approximately 30% increase in the risk for developing CKD in men [100]. Another study examining a hypertensive population found the association between obesity and developing CKD to be significant even after adjusting for differences in blood pressure and diabetes, among other covariates [101]. Proposed mechanisms for the increased risk of CKD in obese patients include alterations in renal haemodynamics possibly from increased salt intake [102], to inflammation and oxidative stress [51, 103].

Multiple studies have found that weight loss is associated with reduction of levels of albuminuria [104, 105]. Bariatric surgery in particular has been found to be the most effective at reducing hyperfiltration compared to non-surgical interventions such as low-calorie diets or exercise; however, these uncontrolled surgical trials included a significant number of patients without significant microalbuminuria at baseline [106]. GLP-1 receptor analogues are a key class of weight loss medications that, as mentioned above, slow progression of albuminuria and prevent cardiovascular events in diabetic patients [80–82]. RAAS blockade using ACEi or ARB therapy has also been shown to decrease proteinuria to 30%–80% of baseline in patients with obesity-related glomerulopathy [107]. Animal studies of antioxidants such as SS-31, lycopene, and melatonin show promising novel targets for improving obesity-related glomerulopathy but require further research to evaluate efficacy and safety for human therapy [107].

Dietary factors

Growing evidence have demonstrated the role of adhering to healthy dietary patterns (i.e. diet rich in vegetables, fruits, legumes, nuts, whole grains, fish, and low-fat dairy; and lower intake of red and processed meats, sodium, and sugar-sweetened beverages) in the prevention of CKD and its progression [108, 109], including plant-dominant low protein (PLADO) diets. Concurrent lower production of dietary acid load, uremic toxins by the gut microbiota, such as trimethylamine n-oxide (TMAO), indoxyl sulphate, and p-cresyl sulphate, and higher intake of important nutrients may be driving this protective association between healthy diet with kidney health vis-a-vis improved glycaemic control, blood pressure control, weight management, and cardiovascular risk reduction [110].

While the underlying mechanisms have not been fully elucidated, recent studies have shown biologically plausible evidence of the association between healthy diets and lower risk of CKD (Fig. 2). First, plant-derived foods (i.e. vegetables, fruits,

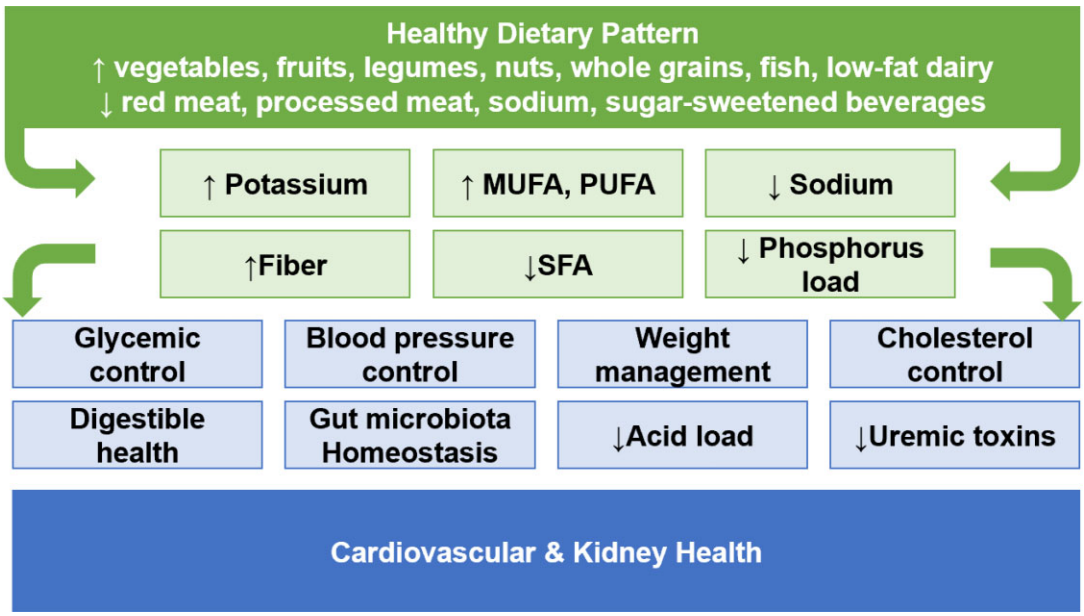

Figure 2: Dietary risk factors of CKD. Abbreviations: MUFA; mono-unsaturated fatty acid, PUFA; poly-unsaturated fatty acid, SFA; saturated fatty acid.

legumes, nuts, whole grains) have higher content of dietary potassium and fibre. Given that potassium plays an important role in critical cell functions including muscle contraction and cardiac conduction, prescribed diets that are rich in potassium, such as the 'Dietary Approaches to Stop Hypertension' (DASH) diet, have been shown to attenuate cardiovascular risk and thus could potentially improve kidney health [111]. Dietary fibre is needed to process/absorb nutrients, as well as micronutrients (antioxidants), and contributes to improved blood pressure, glycaemic control, dyslipidaemia, gastrointestinal motility/constipation, and gut microbiota composition, which may reduce other CKD risk factors such as obesity and diabetes [112]. Second, nuts and fish, which are key components of the Mediterranean diet, bear healthier types of dietary fat (i.e. high mono- and poly-unsaturated fatty acid and lower saturated fat content), which could improve kidney health through improving plasma lipid profiles, insulin resistance, and high blood pressure [113]. Third, despite ongoing controversy with regards to reverse causality at extremely low levels of dietary sodium intake, greater sodium consumption may be detrimental with respect to CKD progression due to increased blood pressure and extracellular volume [114]. Fourth, given that observational studies in both the general and CKD populations have shown that the higher dietary phosphorus intake and elevated serum phosphorus levels are associated with increased risk of cardiovascular disease, phosphorus from plant-derived foods are less likely to contribute to dietary phosphorus burden. For example, dietary phosphorus from plant-based foods typically occurs in the form of phytates and have much lower bioavailability due to lack of the degrading enzyme phytase in humans [115].

Smoking

Smoking's toxic effects are well known, affecting nearly all organs, including the kidneys [116]. With an estimated 30.8 million people who are current smokers, a significant portion of the population is at risk of CKD [117]. Studies have shown that smoking causes direct kidney injury through oxidative stress mediated nephrotoxicity, and indirect kidney injury by increasing the risk of developing aforementioned risk factors such as diabetes and hypertension [118, 119]. In addition, smoking synergistically accelerates the development and progression of CKD in patients with pre-existing CKD risk factors [120]. Overall, smoking has been associated in a dose-dependent manner with new-onset CKD and progression of kidney disease [121, 122]. Smoking cessation drastically improves health-related quality of life and well-being [123], and various pharmacotherapeutic interventions for smoking cessation have been implemented in the non-CKD population (Table 3). However, studies have shown that more than 20 years of abstinence in former smokers are required to decrease the risk of new-onset smoking-associated CKD, emphasizing the lingering adverse effects of smoking [121, 124].

Environmental and genetic

CKDu/Mesoamerican nephropathy

There are specific regions of the world where healthy populations develop CKD without the apparent aforementioned risk factors. This phenomenon is described as CKD of unknown causes (CKDu). CKDu was first documented in El Salvador, and later found in rural populations of the Pacific Ocean coastline of southern Mexico and Central America, often collectively called Mesoamerican nephropathy [125]. Similar cases of CKDu were also described in other parts of world, such Sri Lanka and India, respectively, referred to as Sri Lanka nephropathy and Uddanam nephropathy [126, 127].

The aetiology of CKDu remains debatable. Currently, there is no universally agreed aetiology to the disease. However, based on epidemiologic studies of at-risk populations, commonly found to be agricultural farmers working under intense heat and strenuous working conditions, findings suggest repeated episodes of dehydration and heat stress result in volume depletion. Decreased volume status activates the RAAS to increased renal tubular water and salt reabsorption and diversion of renal blood flow via renal vasoconstriction. Permanent

Table 3: Pharmacological treatment for smoking cessation.

	Dosing	Renal adjustment	Adverse reactions	Precaution
Bupropion	150 mg once daily for the first three days, increase to 150 mg twice daily afterward	eGFR 15–60: maximum 150 mg daily Avoid in eGFR $\leq$ 15	Nausea, constipation insomnia, headache, tachycardia, weight loss (benefit)	Avoid in patients with a history of seizures, anorexia nervosa or bulimia, psychiatric disorder, suicidal thoughts/behaviour or prescribed monoamine oxidase inhibitors
Varenicline	Day 1–3: 0.5 mg once daily Day 4–7: 0.5 mg twice daily Day 8–end: 1.0 mg twice daily Minimal duration of treatment 12 weeks	eGFR $\leq$ 30: starting dose 0.5 mg once daily, titrate as needed to maximum dose of 0.5 mg twice daily	Nausea, insomnia, abnormal vivid dreams, headache	Avoid in psychiatric disorders or suicidal behaviour
Nicotine Patch	>10 cigarettes/day: 12 mg/day for 6 weeks, 14 mg/day for 2 weeks, followed by 7 mg/day for 2 weeks $\leq$10 cigarettes/day: 14 mg/day for 6 weeks, followed by 7 mg/day for 2 weeks	No specific adjustment recommendation Caution in severe kidney disease	Skin irritation, headache, abnormal vivid dreams	Avoid in patients with a recent heart attack (in 2 weeks), angina

kidney injury arises from renal hypoperfusion caused by recurrent episodes of volume depletion [128]. With global warming, temperature-driven volume depletion is expected to increase. As a result, new cases of CKDu will probably be observed in regions previously not documented [129].

Other suggested CKDu risk factors including toxic elements used in agriculture and frequent self-usage of nonsteroidal anti-inflammatory drugs have been studied. However, there is no conclusive evidence yet to support a correlation between CKDu and these proposed risk factors [130].

Apol1

CKD is associated with both genomic and environmental risk factors, with heritability estimated to be 30%–75%. Genetic disorders such as COL4A5 Alport syndrome or PKD autosomal dominant polycystic kidney disease have been well studied with causal links [131]. However, a well-established correlation for CKD and African-Americans lacked evidence to support genetic deposition. With the introduction of genome-wide association studies, Apolipoprotein L1 gene (APOL1) has been strongly associated with CKD in African-Americans [132].

APOL1 is one of six members of APOL gene located on chromosome 22 and encodes a protein that functions as part of the immune system to fight against parasitic infections, such as African trypanosomes [133]. As African trypanosomes are primarily found in Africa, variants to confer protection were selected and disseminated throughout the African population, resulting in the observation of predisposing APOL1 variant alleles seen only in African ancestry [134].

The pathogenesis of risk alleles to the development of CKD remains under investigation, with proposed molecular mechanisms to be a cytotoxic injury to podocytes from mitochondrial dysfunction or lysosomal rupture, leading to nephropathy [135]. However, the presence of risk alleles does not result in CKD, as only 20% of the African-American population with risk alleles develop nephropathy, suggesting contributing environmental factors [136]. The strongest environmental factor associated with APOL1 associated CKD is HIV infection. As APOL1 is part of the immune system, HIV indirectly increases APOL1 expression through direct upregulation of the immune system such as interferon [137]. Other viral infections (i.e. JC virus) or non-infectious diseases (i.e. systemic lupus) that upregulate the immune system have also been associated with APOL1 associated CKD [137–139]. While pharmaceuticals to treat genetic conditions such as APOL1 are currently scarce, there is an ongoing clinical trial for VX-147 for adults with APOL1-mediated proteinuric kidney disease [140].

Herbal nephropathy

Herbal medicine, which consists of plant-derived products, is widely used across the globe, estimated to be used in up to 75% of the world population [141]. Despite its popularity, usage of herbal medicine can result in kidney injury. Multiple mechanisms have been proposed, including direct nephrotoxicity, nephrolithiasis, and rhabdomyolysis [142]. A well-documented nephrotoxic agent found in herbal medicine is aristolochic acid, found in the Artistolochiaceae plant and used mainly in Chinese herbal medicine. It leads to interstitial fibrosis with loss of renal tubules and increased risk of urothelial carcinoma [143]. In addition to the direct nephrotoxic effect of herbal medicine, due to poor regulation over herbal medicine, incorrect processing or storage can introduce additional nephrotoxic agents [142]. Auramine O dye, a carcinogenic dye, has been used for colouring herbal medicine products, and can cause kidney and liver toxicity when consumed [143].

CONCLUSION

In summary, CKD is a major public health problem engendered by various modifiable and non-modifiable risk factors spanning across cardiovascular, endocrine, lifestyle, and genetic/environmental domains. Understanding the major determinants of CKD and the clinical phenotype of high-risk populations are essential for prevention, improved detection,

and earlier implementation of interventions that mitigate progression. With the emergence of new pharmacotherapies, diagnostic tools, and public health initiatives that are directing greater attention towards CKD in the global health agenda, further efforts are needed to improve access to these evidence-based interventions across high-risk groups and vulnerable populations.

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DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

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