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Strategies to prevent kidney disease and its progression

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The 2020 World Kidney Day campaign highlights the importance of prevention of chronic kidney disease. Various strategies and therapies are available to prevent disease before its onset (primary prevention), during early disease stages (secondary prevention) and for effective management of established disease to prevent dialysis (tertiary prevention).

Estimates suggest that 800 million persons might have chronic kidney disease (CKD), with the current global CKD prevalence being between 11 and 13% of the world population[1]. CKD is an irreversible disease state without a cure; its severity often worsens over time, and it is associated with clinically significant comorbidities and adverse outcomes. Hence, the global burden of this non-communicable disease is immense. Patients with the most severe form of CKD (that is, stage 5 or end-stage kidney disease (ESKD)) will have a short life expectancy unless they receive kidney replacement therapy in the form of dialysis or kidney transplantation. Globally, 3 million people currently have ESKD, and their lives depend on expensive dialysis therapy[2,3].

Despite the vastness of the global burden of CKD and its overwhelming costs, little effort seems to be focused on preventive measurements to avoid CKD and its progression to ESKD. Thus, the 2020 World Kidney Day campaign seeks to highlight the importance of prevention under the theme that CKD can be prevented and its progression to ESKD can be delayed[4]. For CKD, the term 'prevention' can be understood in the context of health-related interventions across three distinct categories: primary, secondary and tertiary prevention (TABLE 1).

Primary prevention of CKD

The main goal of primary prevention of CKD is to prevent disease in those who do not have it. Additional targets of primary prevention include effective screening interventions to identify and manage risk factors for CKD and educating the population at large, including health-care providers and policymakers. A relevant concept that is distinct from primary prevention is so-called primordial prevention, which relates to even more upstream interventions that aim to prevent the emergence of risk factors for CKD. For example, in many regions of the world, including both developing and developed countries, the leading risk factor for CKD is adult-onset diabetes mellitus, which might account for half or an even higher proportion of de novo CKD burden. In most populations, obesity is the hallmark of emerging or pre-existing diabetes. Targeting obesity is both a primordial prevention, that is, to prevent diabetes, and a primary prevention, given that obesity might lead to CKD independently of causing diabetes[5]. Both obesity and diabetes can lead to glomerular hyperfiltration, which can be the first sign of impending kidney injury.

Hypertension is the second most common aetiology of CKD and is also associated with metabolic syndrome. Cancer-related or living donor nephrectomy can increase the risk of CKD by several folds, and preventive measures are recommended for persons with solitary kidney[6]. Among interventions to adopt in primary and primordial prevention of CKD is lifestyle modification, including physical activity to avoid or manage obesity. Emerging data suggest an important role of diet, including avoidance of excessive sodium and protein intake, which can cause or worsen glomerular hyperfiltration. In patients with diabetes or hypertension, optimizing glycaemic and blood pressure control should be pursued, respectively. Emerging epidemiological data suggest the preventive role of adequate hydration, given the example of Mesoamerican nephropathy (also known as CKD of unknown origin), which might result from recurrent instances of volume depletion in a hot climate[7].

Secondary prevention of CKD

Given the often asymptomatic nature of CKD in its early stages, the secondary prevention of CKD focuses on screening measures to detect early signs of CKD including microalbuminuria, glomerular haematuria and mild elevations in kidney filtration markers such as serum creatinine and cystatin C levels. Relevant to this goal are patients with stage 1 or 2 CKD, that is, positive test results for albuminuria with an estimated glomerular filtration rate (eGFR) >60 ml/min/1.73 m^2 body surface area (BSA), as well as patients with or without albuminuria with early CKD stage 3A, that is, eGFR of 45–60 ml/min/1.73 m^2 BSA. For these patients, the goal of secondary prevention is to prolong the functioning life of the kidney and to slow CKD

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Table 1 | **Approach to preventive strategies in CKD**

Approach	Main goal	Additional targets	Alarming signs	Risk factors to target	Interventions
Primary prevention	Avert kidney disease	Manage risk factors for kidney disease; educate on primordial prevention	Glomerular hyperfiltration	Diabetes; hypertension; obesity; solitary kidney; genetic risks; other risk factors	Support lifestyle modifications with moderate physical activity; provide dietary advice including avoidance of high sodium and excessive protein intake; prevent and manage obesity; improve glycaemic and blood pressure control; identify genetic risk factors; ensure adequate hydration
Secondary prevention	Identify early disease	Slow CKD progression; prolong kidney health	Emerging or worsening albuminuria; declining eGFR	Proteinuria; uncontrolled hypertension; poor glycaemic control; high protein intake	Manage proteinuria; encourage low-sodium and low-protein diet; encourage more plant-based sources for dietary protein; identify and offer effective pharmacotherapy; individualize therapy; identify and manage additional CKD risk factors; explore integrative and alternative approaches
Tertiary prevention	Avoid kidney failure	Delay dialysis transition; preserve the remaining kidney function	Worsening uraemic signs and symptoms	AKI events and AKI risk factors; worsening cardiac function (cardiorenal syndrome)	Manage uraemic symptoms and comorbidities; manage fluid and sodium retention; manage cardiovascular risk factors; explore novel kidney preservative and supportive therapies

Primary prevention is to avert emergence of de novo chronic kidney disease (CKD), secondary prevention aims to identify CKD as early as possible and tertiary prevention strives to avoid end-stage kidney disease, also known as kidney failure. AKI, acute kidney injury; eGFR, estimated glomerular filtration rate.

progression. Two important targets are mitigating the severity of proteinuria and lowering intraglomerular pressure using both pharmacotherapy (such as angiotensin pathway modulators) and dietary interventions (including a low-salt and low-protein diet to achieve a total protein intake target of 0.6–0.8 g/kg ideal body weight per day with more than half of it being from plant-based sources)[8]. As with primary prevention, hypertension and diabetes should be controlled to prevent faster CKD progression. Further novel and alternative secondary preventive options are needed, including emerging pharmacotherapy approaches and individualized therapy.

Tertiary prevention of CKD

The main goal of tertiary prevention of CKD is to avoid kidney failure in those with moderate to advanced CKD, that is, eGFR <45 ml/min/1.73 m^2 BSA, and to delay initiation of dialysis if possible and without causing harm. Among important tertiary preventive measures is the prevention of acute kidney injury (AKI), given that superimposed AKI events in advanced CKD might not only accelerate progression to ESKD but can also lead to inevitable need for dialysis, which can then result in hypotensive episodes during dialysis therapy with superimposed ischaemic injuries to kidneys. Worsening cardiac function in the form of haemodynamic cardiorenal syndrome and fluid retention is another risk factor for accelerated CKD and transition to dialysis for fluid management. Hence, nephrotoxic agents or hypotensive events that can cause AKI should be avoided, and coexisting heart failure should be controlled. Uncontrolled and recurrent hyperkalaemia events pose another problem, although the development of novel potassium-binding therapies might reduce or prevent these events.

Effective management of CKD comorbidities might delay the need for dialysis therapy, including management of anaemia, mineral-bone disorders and metabolic acidosis. Whereas low-protein diets should be continued to limit the burden of nitrogenous end-products and to better control uraemia, liberalizing dietary intake during episodes of AKI or protein-energy wasting might be imperative[8]. Conservative management of uraemia and preservative management of residual kidney function might be pursued with the advent of novel therapies for uraemic symptoms such as pruritus, nausea, vomiting and muscle cramps[9]. However, refractory uraemic encephalopathy and uraemic pericarditis often prompt transition to dialysis therapy, although in the past few years a gradual and incremental transition to dialysis has been on the rise, including with once-weekly to twice-weekly haemodialysis, so that residual kidney function can be preserved longer[10]. An important goal of tertiary prevention should be to explore and develop novel kidney preservative and supportive therapies.

Future opportunities

Strong consensus exists among opinion leaders about reinforcing screening strategies for early detection of CKD (that is, secondary prevention); however, the primary prevention of de novo CKD and management of its risk factors is not routinely pursued, and trial-based evidence to support routine screening and monitoring for CKD risk is lacking. In addition, opportunities for tertiary prevention have been overlooked, at least until the past few years, with previous guidelines suggesting earlier rather than later transition to dialysis and using full-dose dialysis at the start instead of incremental transition to dialysis. As we enter the new decade, new opportunities are bestowed upon us to more effectively prevent CKD, its progression and ESKD.

1. Hill, N. R. et al. *PLoS One* **11**, e0158765 (2016).
2. Bello, A. K. et al. *Kidney Int. Suppl.* **8**, 41–51 (2018).
3. Bello, A. K. et al. *BMJ* **367**, l5873 (2019).
4. Li, P. K.-T. et al. *Kidney Int.* **97**, 226–232 (2020).
5. Kovesdy, C. P. et al. *J. Ren. Nutr.* **27**, 75–77 (2017).
6. Tantisattamo, E. et al. *Kidney Int Rep.* **4**, 1205–1218 (2019).
7. Wesseling, C. et al. *Environ Res.* **147**, 125–132 (2016).
8. Kalantar-Zadeh, K. & Fouque, D. *N. Engl. J. Med.* **377**, 1765–1776 (2017).
9. Rhee, C. M. et al. *Curr. Opin. Nephrol. Hypertens.* **29**, 92–102 (2020).
10. Murea, M. et al. *Kidney Int. Rep.* https://doi.org/10.1016/j.ekir.2019.11.014 (2019).

Competing interests

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