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HOW CAN WE HALT-CKD IN PRIMARY CARE? CLINICAL CARE PATHS TO MANAGE CHRONIC KIDNEY DISEASE

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ABSTRACT

Chronic kidney disease (CKD) is a major health problem in Singapore, and its incidence is projected to rise. Slowing the progression of CKD is paramount in enabling patients to live longer without complications or the need for kidney replacement therapy, allaying the health and economic burden of CKD on individuals and the society. Effective treatment strategies comprise of lifestyle, dietary, and medical management, which include dietary sodium restriction, physical activity, smoking cessation, blood pressure and glucose control, and use of renin-angiotensin system inhibitors to reduce albuminuria. The Holistic Approach in Lowering and Tracking Chronic Kidney Disease (HALT-CKD) programme is a concerted effort to delay the progression of CKD through a multi-faceted, integrated approach. Here, we outline the rationale and aims of these recommendations, provide practical tips for implementing these interventions, and highlight future opportunities in our ongoing battle against CKD.

Keywords: Chronic kidney disease, care path, lifestyle modifications, medical management, progression

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INTRODUCTION

Chronic kidney disease (CKD) remains a major public health problem globally and in Singapore. It is predicted that the incidence and prevalence of CKD will rise sharply[1], given an aging population coupled with growing incidences of diabetes, hypertension, and obesity. CKD is generally irreversible, and progressive CKD is associated with adverse clinical outcomes, including development of end-stage kidney disease (ESKD), increased risk of cardiovascular events, all-cause hospitalisation, and reduced life expectancy.[2-5]

In individuals diagnosed with CKD, slowing the progression of CKD can be achieved through a range of lifestyle modifications and medical interventions. These lifestyle, dietary, and pharmacological strategies, which include dietary sodium restriction, smoking cessation, physical activity, blood pressure and glucose control, and use of renin-angiotensin system inhibitors (RASi), are broadly applicable, regardless of the aetiology of the CKD. Indeed, in many CKD patients, these strategies form the mainstay of management to slow the progression of CKD.

Primary care physicians are pivotal to the care of CKD patient. Many issues in CKD care overlap with those of diabetes and hypertension. Identifying and managing CKD in the early stages (prior to nephrology referral) can improve patient outcomes. Since 2017, Singapore has embarked on the Holistic Approach in Lowering and Tracking Chronic Kidney Disease (HALT-CKD) programme as a concerted effort to delay the progression of CKD through an integrated, multi-faceted approach. The HALT-CKD programme focuses on a series of lifestyle modifications and medical interventions that are broadly applicable to all patients across CKD stages 1 to 4. This article outlines the rationale and aims of these recommendations, provide practical tips for implementing these interventions, and highlight future opportunities in the fight against CKD.

LIFESTYLE MODIFICATIONS

Low-salt diet

The modern Western diet is heavily influenced by rapid urbanisation and changing lifestyles. Our diet now consists of large amounts of processed food and energy-dense foods that are high in saturated fat, trans fat, sugar, and salt, resulting in an adverse impact on the risks of non-communicable diseases.[6] Salt, the primary source of sodium, contributes to hypertension, which is a known risk factor for CKD and its progression. A Cochrane systematic review demonstrated that dietary sodium reduction results in reductions in blood pressure in those with CKD.[7] The 2021 Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline on Management of Blood Pressure in CKD recommends targeting salt intake to <90 mmol (<2g) per day of sodium among patients with CKD and hypertension.[8] This would be equivalent to less than a teaspoon of salt per day. While dietician referral is not always available, examples of practical advice for patients include not adding salt during food preparation, not having a saltshaker on the table, and limiting the consumption of salty snacks. Patients should be encouraged to select food products that bear the "Lower in Sodium" Healthier Choice symbol, as these food products contain at least 25 percent less sodium than similar products without the symbol. Natural flavourings such as herbs, spices, and other ingredients may be used as salt substitutes to lower dietary sodium intake. It is important to educate patients, especially those with advanced CKD, that they are prone to hyperkalaemia (due to decreased renal excretion and use of

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RASi that can raise serum potassium levels) and hence should avoid salt substitutes that contain potassium.

Physical activity

It is well established that physical activity lowers blood pressure, helps control weight, improves diabetes control, and improves overall cardiovascular health.[9,10] In turn, these are associated with an improvement in life expectancy in patients with CKD. There is however, also evidence that physical activity is associated with slower rates of decline in renal function.[11] KDIGO recommends moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week in patients with CKD and hypertension.[12] The level of physical activity has to be compatible with the cardiovascular and physical tolerance of individual patients, as it is recognised that a significant proportion of patients with CKD are frail or have severe cardiorespiratory disease, which limits their participation in vigorous physical activities.

Smoking cessation

Tobacco exposure is also associated with increased risk of progression of kidney disease.[13] Proposed underlying mechanisms leading to kidney damage are sympathetic activation affecting blood pressure and renal haemodynamic, and oxidative stress leading to endothelial cell dysfunction.[14] As smoking cessation decreases proteinuria in patients with CKD and slows progression to ESKD, current smokers should be counselled on the benefits of smoking cessation and its effects on kidney disease, in addition to its other health benefits. Patients may also enrol in the "I Quit Programme" organised by the Health Promotion Board, which incorporates a multi-pronged approach of counselling, medications such as varenicline and bupropion, and nicotine replacement therapy.

MEDICAL INTERVENTIONS

Initiation and optimisation of renin-angiotensin system inhibitors

The initiation and optimisation of renin-angiotensin system inhibitors (RASi) have been the cornerstones of kidney protection strategy over the past decades. The salutary effect of RASi in CKD is driven by its reduction of intra-glomerular pressure and reduction of albuminuria, in addition, to its blood pressure-lowering effects. Previous landmark studies have shown that the use of RASi has a protective effect in reducing the progression of CKD, both in patients with[15,16] or without[17,18] diabetes.

Importantly, the dose of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blocker (ARB) should be titrated to the maximally tolerated approved dose to maximise the benefits in albuminuria reduction, blood pressure control, and retarding kidney disease progression. Several strategies may help patients achieve up-titration and optimisation of their RASi: namely, they should be counselled on a low potassium diet or the addition of thiazide/loop diuretics to avoid hyperkalaemia, and it may be necessary to decrease or stop other blood pressure lowering agents, e.g., calcium channel blockers if low blood pressure is preventing the up-titration of RASi. It is also worth noting that several studies have shown that dual blockade with ACEi and ARB results in an increased risk of adverse outcomes, including hyperkalaemia and acute kidney injury, with no clear benefit. Hence, the ACEi/ARB combination should be avoided.[19,20]

Blood pressure-lowering agents

Blood pressure reduction lowers the risk of progression of kidney disease and reduces the risk of cardiovascular events in patients with CKD. The blood pressure target is recommended to be less than or equal to 140/90 mmHg in CKD patients without albuminuria, and less than or equal to 130/80 mmHg in CKD patients with albuminuria.[21]

More recent guidelines and evidence suggest that a systolic blood pressure target of less than 120 mmHg in people with CKD may reduce the risks of cardiovascular event and mortality (but not kidney disease progression *per se*).[8,22] However, in some patients, such intensive blood pressure lowering may have a negative haemodynamic effect and paradoxically induce a more rapid decline in kidney function. Also, it is important to consider patients' comorbidities and frailty, and identify patients who are at increased risk of adverse events with intensive blood pressure control. Overall, we do not recommend a systolic blood pressure target of less than 120 mmHg for all patients. Rather, we suggest an individualisation of a lower blood pressure targets in patients where the benefits outweigh the risks.

Glycaemic control

Glucose-lowering therapy and good glycaemic control can retard the progression of kidney disease by reversing the metabolic abnormalities pathognomonic of diabetes mellitus. In the *post hoc* analysis of a large clinical trial, patients treated to a lower target of HbA1c had a lower risk of kidney failure.[23] In general, HbA1c should be targeted at less than 7.5 percent in diabetic patients with CKD, balancing the risks of micro- and macrovascular complications and the development of hypoglycaemia, especially in the elderly or patients with multiple conditions.

In addition to a lower HbA1c target, it is now clear that specific classes of glucose-lowering therapies may have additional benefits in preventing the progression of kidney disease (see Emerging Treatment, below).

Referral to nephrology

Patients with advanced CKD should be referred to nephrology (although exact timing may vary with the

patient's status), with shared care between the primary care physician and nephrologist. The nephrologist's role will include management of complications of CKD, e.g., anaemia requiring erythropoietin replacement, and planning kidney replacement therapy and transplant evaluation. The decision to begin kidney replacement therapy is based on the presence of symptoms and not solely on level of glomerular filtration rate. A shared decision-making approach, in which early patient education and active contribution to the decision-making by the patient, is best, and the patient's preferences for conservative medical management of ESKD should be discussed and honoured.

EMERGING TREATMENT

In the past two decades, the armamentarium for retarding progression of CKD has been centred around the use of RASi. However, several recent clinical trials have demonstrated the efficacy of novel therapeutic agents that can further slow the progression of CKD when used together with RASi. In addition, there is emerging evidence of the benefits of a plant-based diet with regards to prevention of CKD.

Plant-based diets

A growing body of evidence has emerged for the adaptation of plant-based diets as both a primary and secondary prevention of CKD. Plant-based diets have a low net endogenous acid load and can mitigate metabolic acidosis in patients with CKD. As phosphorus is not as efficiently absorbed from plant sources, this reduces the risk of hyperphosphatemia, which is often a concern in patients with CKD. A prospective observational study has shown that plant-based diets were associated with a lower risk of decline in estimated glomerular filtration rate (GFR) compared with meat-based diets.[24]

Examples of dietary patterns that align with the concept of plant-based diets are the Dietary Approaches to Stop Hypertension (DASH) and Mediterranean diet. The DASH diet, which is high in fruits, vegetables, and low-fat dairy products, and with reduced saturated and total fat, is widely recommended to manage hypertension and has also been shown to reduce progression to ESKD.[25] However, it is important to note that the DASH diet may not be appropriate for patients with advanced CKD due to the potassium load from salt substitutes, as discussed earlier.

SGLT2 inhibitors

Several recent large randomised controlled trials have demonstrated the role of sodium glucose cotransporter 2 (SGLT2) inhibitors in conferring kidney and cardiovascular protection, in addition to its glucose-lowering effects in patients with diabetes.[26,27] By blocking the reabsorption of sodium and glucose in the proximal tubule, SGLT2 inhibitors induce natriuresis and hence reduce intraglomerular pressure. This, in turn, reduces glomerular hyperfiltration and slows the rate of progression of kidney disease. SGLT2 inhibitors may also have direct anti-fibrotic and anti-inflammatory effects. Importantly, evidence suggests that the kidney-protective effects of SGLT2 inhibitors are similarly extended to CKD patients without diabetes.

The 2020 KDIGO Clinical Practice Guideline for Diabetes Management in CKD recommends SGLT2 inhibitors (alongside metformin) as the first line of therapy in diabetic CKD patients with eGFR ≥ 30ml/min per 1.73m^2.[28] SGLT2 inhibitors are generally well tolerated but patients should be educated about potential side effects of genital mycotic infections, volume depletion, and euglycemic ketoacidosis. Patients should also be educated on good genital hygiene, adequate hydration, and stopping SGLT2 inhibitors as part of diabetes sick day management.

Mineralocorticoid receptor antagonist

Finerenone, a nonsteroidal, selective mineralocorticoid antagonist, was recently approved by the United States Food and Drug Administration for treatment of diabetic kidney disease, after a landmark trial demonstrated that its use lowers the risk of CKD progression and cardiovascular events in diabetic CKD patients.[29] Interestingly, the use of finerenone combined with a single RASi was not associated with a higher risk of acute kidney injury-related events, which was seen in the previous kidney outcome trials targeting dual RASi. Serum potassium levels should be monitored when prescribing a mineralocorticoid receptor antagonist due to its risk of hyperkalaemia in a small proportion of patients.

Sodium bicarbonate and veverimer

Metabolic acidosis is a common complication of CKD, and leads to muscle catabolism, bone resorption, and progression of CKD. Sodium bicarbonate ameliorates these deleterious effects of metabolic acidosis and has been shown to improve kidney outcomes and survival.[30] However, its use is limited by the provision of sodium to patients with hypertension and sodium retention. Veverimer, a non-absorbed polymer that selectively binds and removes hydrochloric acid from the gastrointestinal lumen, has shown promise in increasing serum bicarbonate concentration without the unfavourable effect of sodium load. Patients who received veverimer also showed a significant improvement in physical fitness.[31]

CLINICAL CARE PATHS

The key components to slowing progression of CKD described here can be integrated into a clinical care path, providing the mainstay of CKD management in primary care (Figure 1). These are broadly applicable regardless of underlying aetiology and is especially critical in the early stages of CKD. As the landscape for new therapeutics in CKD continues to expand with novel therapeutics such as SGLT2 inhibitors and other therapies under investigation, new treatments and recommendations should provide increased impetus to identify CKD patients who may derive large benefits from these therapies. Nonetheless, it should

be emphasised that the broad treatment strategies of lifestyle and dietary modifications, blood pressure, glucose control, and optimisation of RASi discussed will continue to form the backbone of CKD management.

SUMMARY

Chronic kidney disease is a major health problem in Singapore. However, with concerted efforts to implement effective treatment strategies that target both lifestyle and medical risk factors, we can slow the progression of CKD, enabling patients to live longer without complications or the need for kidney replacement therapy.

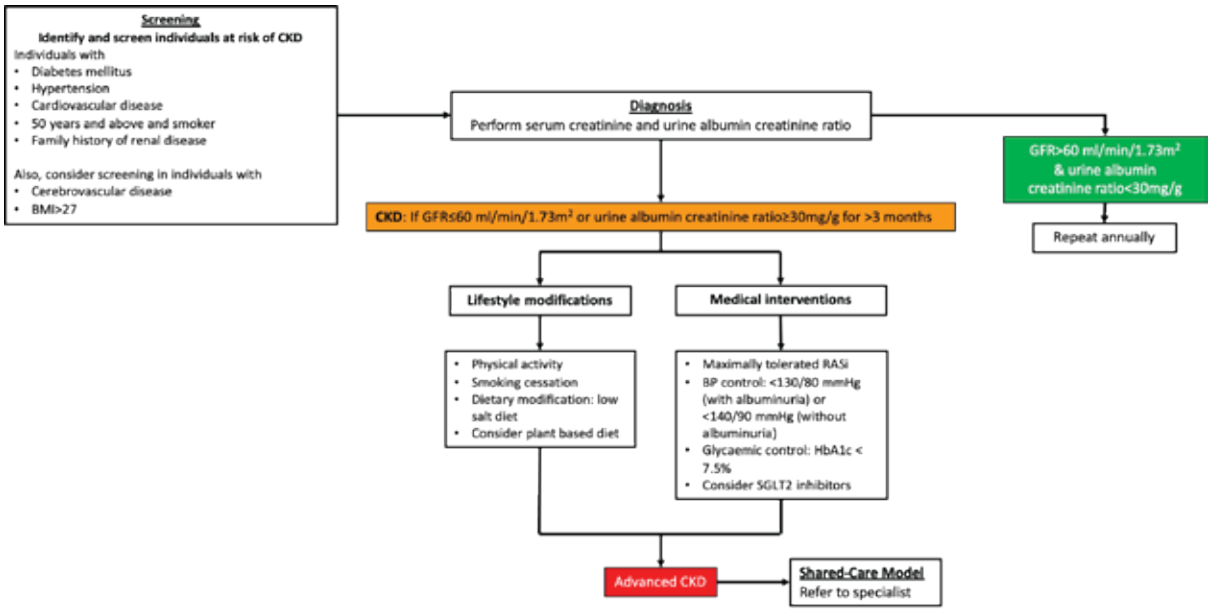
Table I: Lifestyle Modifications to HALT-CKD in Primary Care

Lifestyle modification	Recommendations	Practical tips
Low salt diet	Target salt intake of less than 2000 mg of sodium per day	• Avoid adding salt during food preparation; avoid table salt • Salt substitutes, e.g., herbs, spices, and other natural flavourings • Choose foods with "Lower in Sodium" Healthier Choice Symbol
Physical activity	Moderate intensity physical activity of >150 minutes (cumulative) per week	Target exercise to a level compatible with patients' cardiovascular and physical tolerance, and in consideration of patient's general health
Smoking cessation	All patients with CKD should stop smoking	I Quit Programme – personalised quit journeys incorporating counselling, aids such as medications, and nicotine replacement therapy
Plant-based diet	Increase consumption of plant foods (fruit, vegetables, nuts, seeds, oils, whole grains, legumes, and beans)	• Go meatless for 1-2 meals per week • Limit processed meats and replace animal sources of protein (meat, poultry, and fish) with plant sources of protein (tofu and legumes) during meals

Table II: Medical Management to HALT-CKD in Primary Care

Medical intervention	Recommendations	Practical tips
Renin-angiotensin system inhibitors	Start and optimise ACEi or ARBs in all patients	• Low potassium diet and/or thiazide/loop diuretic, to avoid hyperkalaemia • Stop/decrease calcium channel blocker if BP is low
BP control	Aim for ≤140/90 mmHg (without albuminuria) or ≤130/80 mmHg (with albuminuria)	• Preferred BP lowering agent is ACEi or ARB • May target systolic BP ≤120 mmHg in selected patients for additional cardiovascular protection
Glycaemic control	Aim for HbA1c ≤ 7.5 percent	• Consider specific classes of glucose-lowering treatment e.g. SGLT2 inhibitors, which delay CKD progression • Individualise target to patient's condition, taking care to avoid hypoglycaemia

Figure 1: Clinical Care Path to HALT-CKD in Primary Care



List of Abbreviations

ACEi – angiotensin-converting enzyme inhibitors

ARB – angiotensin II receptor blocker

BP – blood pressure

BMI – body mass index

CKD – chronic kidney disease

GFR – glomerular filtration rate

SGLT2 – sodium glucose cotransporter 2 inhibitors

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LEARNING POINTS

- **Slowing the progression of renal function decline is a key treatment aim in chronic kidney disease, as this is paramount in enabling patients to live longer without complications or the need for kidney replacement therapy.**
- **Dietary sodium restriction, physical activity, smoking cessation, blood pressure and glucose control, and use of renin-angiotensin system inhibitors to reduce albuminuria, when integrated together as a multi-faceted approach, is effective in delaying the progression of CKD.**
- **These current treatment strategies will remain the mainstay of CKD management but newer therapeutics are expected to alter the future landscape of the management of CKD patients.**