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MAKING SENSE OF CHRONIC KIDNEY DISEASE IN PRIMARY CARE PART 2 - MANAGEMENT

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ABSTRACT

Chronic kidney disease (CKD) is common worldwide and in Singapore. The primary care physicians play an important role in managing patients with CKD, especially in the early stages of CKD. The primary objectives of CKD management are (1) slowing down the progression of CKD, (2) managing the complications of CKD, and (3) establishing the long-term kidney care plan. The interventions to slow down the progression of CKD are to identify the cause of CKD, use the renin-aldosterone system blocker and the sodium-glucose cotransporter-2 inhibitor in suitable CKD populations, optimise blood pressure and glycaemic control, correct acidosis, avoid acute kidney injury and nephrotoxin, and modify dietary and lifestyle habits. For complications of CKD, the focus is on reducing cardiovascular risk, and managing anaemia, mineral bone disease, electrolytes imbalances and fluid overload. Lastly, there is a need to establish CKD patient's treatment goals and initiate advanced care planning in a patient with progressive CKD to facilitate future care.

Key Words: Chronic kidney disease, management, progression, complications

INTRODUCTION

Patients with chronic kidney disease (CKD) are at risk of progression to end-stage kidney disease (ESKD), increased cardiovascular events and mortality.[1] The prevalence of CKD is high worldwide, ranging from 11 percent to 13 percent.[2] In Singapore, the prevalence of CKD is projected to increase to 24.3 percent by 2035 due to an ageing population and an increasing incidence of diabetes mellitus (DM) and hypertension.[3]

In the early stages of CKD, the majority of the patients are managed by the primary care physicians. Primary care physicians have vast experiences managing chronic metabolic and cardiovascular diseases and are well placed to manage patients with CKD.

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SLOWING THE PROGRESSION OF CHRONIC KIDNEY DISEASE

Identify the cause of chronic kidney disease

The identification and institution of appropriate treatment to the underlying cause of CKD is the initial step in slowing the progression of CKD. In Singapore, the most common causes of CKD are DM (65.8 percent) and chronic glomerulonephritis (14.1 percent).[4] The other causes include hypertension (including renovascular disease), hereditary polycystic kidney diseases, vesico-ureteric reflux, chronic pyelonephritis, obstructive uropathy and previous acute kidney injury. A high index of suspicion is required in identifying chronic glomerulonephritis through the identification of varying clinical features ranging from nephrotic syndrome, nephritic syndrome, haematuria, proteinuria, cellular urinary casts and fast declining estimated glomerular filtration rate (eGFR). Patients with suspected chronic glomerulonephritis require referral to the nephrologist for further assessment, and some may subsequently need immunosuppression therapy.

Use of renin-aldosterone system blockade

The renin-aldosterone system (RAS) blockade has been a cornerstone in the management of diabetic and non-diabetic CKD patients with albuminuria. In this group of patients, the use of an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin II receptor blocker (ARB) has been shown to reduce intraglomerular hypertension and have anti-inflammatory and anti-fibrotic effects in the kidney.[5-7] Multiple studies have shown that RAS blockade slows down the decline of kidney function in proteinuric CKD.[8-10] It is recommended to titrate either ACE-I or ARB to its maximally tolerated approved dose.[11] Due to haemodynamic changes in the glomeruli with the initiation of RAS blockade, there can be an expected increase in serum creatinine by up to 30 percent and possible increase in serum potassium.[12,13] Any increment more than 30 percent in serum creatinine warrant a suspension of the RAS blocker and investigate of cause of acute kidney injury, including renal artery stenosis. It is also prudent to target serum potassium to less than or equal to 5.5mmol/L and educate the patient on low potassium diet.

Use of sodium-glucose cotransporter-2 inhibitor

The sodium-glucose cotransporter-2 (SGLT-2) inhibitor studies in both DM and non-DM CKD patients have shown positive result in reducing adverse CKD outcomes. CREDENCE and DAPA-CKD studies have shown that in diabetic and non-diabetic CKD patients on RAS blockade, the addition of SGLT-2 inhibitor further reduced the risk of kidney failure and cardiovascular events.[14,15]

It is recommended to treat patients with DM and CKD (eGFR at least 30ml/min/1.73m^2 or more) with SGLT-2 inhibitor.[16] Even though promising results have also been reported in non-DM CKD patients in the DAPA-CKD study, there is currently no recommendation on initiating SGLT-2 inhibitor in this group of patients.

Blood pressure targets

Multiple studies have shown that intensive blood pressure control slows progression to kidney failure and reduce cardiovascular events.[17-19] In the Kidney Disease Improving Global Outcomes (KDIGO) 2012 clinical practice guideline for the evaluation and management of chronic kidney disease, the blood pressure control is recommended to be less than or equal to 140/90 in CKD patients without albuminuria, and less than or equal to 130/80 in CKD patients with albuminuria.[11] However, the treatment target for older patients with CKD is controversial, and the treatment goal should be individualised.[20]

HbA1c target

The current KDIGO guideline suggested individualised HbA1c target range from less than 6.5 percent to less than 8.0 percent based on several patient's factors, including the severity of CKD, macrovascular complications, comorbidities, life expectancy, hypoglycaemia awareness, resources for hypoglycaemia management and the propensity of treatment to cause hypoglycaemia.[16] The primary care physicians will have to balance the benefit of targeting lower HbA1c levels which reduce the rate of diabetes complications against the risk of hypoglycaemia and its complications.

Correction of acidosis

The development of metabolic acidosis in patients with CKD is common, especially when the eGFR is less than 30ml/min/1.7m^2. This is due to a decrease in renal ammonium excretion and a positive acid balance. Studies have shown that correction of serum bicarbonate to the normal range (22 to 26 mmol/L) is associated with improved kidney outcomes.[21,22] Hence, it is recommended to initiate oral sodium bicarbonate tablets in CKD patients when the serum bicarbonate is less than 22 mmol/L to maintain serum bicarbonate within the normal range with monitoring of fluid overload, hypokalaemia and hypocalcaemia.[11]

Avoidance of acute kidney injury

Acute kidney injury (AKI) is strongly associated with CKD and its progression.[23,24] Preventing AKI can reduce the risk of CKD progression. Nephrotoxin is one of the preventable causes of AKI. All patients with CKD should be advised on the avoidance of nephrotoxin. Regular administration of nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase 2 (Cox-2) inhibitor is not recommended.[23] Herbal remedies and supplements may contain nephrotoxins (e.g., aristolochic acids, alkaloids, anthraquinones, flavonoids, glycosides and heavy metal contamination), which can cause varying kidney abnormalities, including acute tubular necrosis, interstitial nephritis, nephrolithiasis and Fanconi syndrome.[25]

Dietary control

High sodium intake increases BP and proteinuria, induces glomerular hyperfiltration and blunts the response to RAS blockade. Through decreasing sodium intake, there is moderate to weak evidence to suggest a decrease in risk in cardiovascular disease, stroke and progression of CKD.[26] The KDIGO 2012 guideline recommended lowering sodium intake to less than 90mmol (<2g) per day (corresponding to 5g of sodium chloride).[11]

Excess protein intake leads to accumulation of uremic toxins. Hence, the KDIGO 2012 guideline suggested avoiding high protein intake (more than 1.3g/kg/day) in CKD patients at-risk of progression and lowering protein intake to 0.8g/kg/day in CKD patients with eGFR less than 30ml/min/1.73m^2.[11] Not all proteins are equal too. The Singapore Chinese Health Study shows that red meat intake may increase the risk of kidney failure in the general population.[27]

Lifestyle modifications

Lack of physical activity and obesity (BMI more than 27.5 for Asian population) are associated with increased mortality, morbidity and risk of metabolic disease.[28,29] The KDIGO 2012 recommended targeting moderate-intensity physical activity for at least 150 minutes per week and achieving a healthy weight (BMI 18.5 to 22.9 in Asian population).[11] Smoking cessation is advised. Smoking is associated with increased risk of CKD progression and cardiovascular mortality and morbidity in CKD population.[30]

MANAGING THE COMPLICATIONS OF CHRONIC KIDNEY DISEASE

Cardiovascular Disease Risk

Cardiovascular disease is the most common cause of death in patients with CKD. Both low eGFR and albuminuria are risk factors for cardiovascular events.[31,32] Modifications of cardiovascular risks factors, such as optimisation of blood pressure and glycaemic control, healthy diet, smoking cessation, exercise and weight control, are some of the similar measures that are used to slow down the progression of CKD.

Hyperlipidaemia is an important cardiovascular risk factor in CKD population, similar to the general population. The SHARP study has shown a 15 percent risk reduction in cardiovascular event rate in the CKD group receiving simvastatin plus ezetimibe.[33] It has been also shown that the benefit of statins becomes less pronounced as CKD progressed.[34] The KDIGO 2013 lipid guideline recommends initiating statin treatment in CKD patients more than or equal to 50 years old, and CKD patients more than or equal

to 18 years old with one or more risk factor (DM, coronary artery disease, stroke, or estimated ten-year incidence of coronary death or non-fatal myocardial infarction more than ten percent).[35] The doses of statins are suggested to base on doses that have been shown to be beneficial in randomised trials, which are in the moderate-intensity range (for example, simvastatin 40mg/day, atorvastatin 20mg/day, rosuvastatin 10mg/day and simvastatin/ezetimibe 20mg/10mg/day).[35]

Low-dose aspirin is indicated for secondary prevention of atherosclerotic cardiovascular disease in CKD patients. However, low-dose aspirin is not recommended for primary prevention of atherosclerotic cardiovascular disease for adults who are at increased risk of bleeding (including patients with CKD).[36,37]

Anaemia

The incidence and prevalence of anaemia increase as the kidney function declines. Monitoring for anaemia in asymptomatic CKD patients usually starts when eGFR is less than 60ml/min/1.73m^2 and frequency of monitoring increases as eGFR declines. Apart from anaemia of CKD, one of the more common reversible cause of anaemia in CKD patients is iron deficiency anaemia. However, it is important to approach new or worsening anaemia in CKD patients in a similar fashion to anaemia in non-CKD patients to investigate and treat reversible causes of anaemia. In anaemia of CKD, the overall clinical goals are avoidance of transfusion and its associated complications, and improvement in anaemia-related symptoms. A trial of oral iron therapy can be considered in CKD patients where an increase in haemoglobin concentration is desired, and transferrin saturation is less than or equal to 30 percent, and ferritin is less than or equal to 500ng/ml.[38] The use of erythropoiesis stimulating agents are considered after balancing the potential benefits against the risks, and they are usually initiated by nephrologists in patients with anaemia of CKD after repletion of body iron store.

Mineral Bone Disease

There is progressive deterioration in mineral homeostasis with the decline of the kidney function. This results in abnormalities in phosphorus, calcium, parathyroid hormone (PTH) and vitamin D levels, which ultimately affects bone homeostasis and increases risks of extra-skeletal calcification, fractures, cardiovascular disease and mortality. Monitoring for mineral bone disease in CKD patients usually starts when eGFR is less than 60ml/min/1.73m^2, and serum phosphate, calcium, PTH, vitamin D and alkaline phosphatase are monitored and considered together.[39] It is recommended to lower persistently elevated phosphate and avoid hypercalcemia.[40] Low phosphate diet is recommended for CKD patients with hyperphosphatemia. If the hyperphosphatemia continues to persist or worsen, phosphate binders are suggested. Even though studies have suggested a potential benefit of using non calcium-based phosphate binders in CKD patients with hyperphosphatemia compared to calcium-based phosphate binders, the concern of cost in local setting may result in patients' and physicians' preference to the calcium-based phosphate binders. The management of CKD patients with elevated PTH level involves the correction of vitamin D deficiency or insufficiency, hyperphosphatemia and hypocalcaemia. Vitamin D analogs are not routinely used in non-dialysis CKD patients. They are reserved for severe and progressive hyperparathyroidism in eGFR less than 30ml/min/1.73m^2 and are usually initiated by nephrologists.[41]

Electrolytes Imbalance and Fluid overload

Hyperkalaemia and metabolic acidosis are some of the common electrolyte abnormalities in CKD patients. The frequency of these abnormalities increases with declining kidney function. The management of metabolic acidosis has been discussed earlier. Hyperkalaemia increases the risk of mortality and major adverse cardiovascular events.[42,43] Monitoring of hyperkalaemia is required. For CKD patients with serum potassium persistently more than 5.5mmol/L, discussion on further management with low potassium diet, down-titration of RAS blocker, and/ use of diuretic (with concurrent fluid overload) and sodium bicarbonate (with concurrent CKD related metabolic acidosis) is needed.

Fluid overload in CKD patients tends to occur when eGFR is less than 30ml/min/1.73m^2. It can be associated with mortality, cardiovascular morbidity and faster eGFR decline.[44,45] Fluid overload can occur at higher eGFR range, especially in CKD patients with other comorbidities (e.g., heart failure). Management of fluid overload is to limit sodium and fluid intake and the judicious use of diuretic. Regular clinical examination for fluid status during the consultation is required to optimise diuretic dose titration.

ESTABLISHING LONG-TERM KIDNEY CARE PLAN

It is imperative to establish a long-term kidney care plan for CKD patients who are at risk of progression to kidney failure. In Singapore, the age of reaching kidney failure is increasing.[4] Higher age comes with an increasing comorbidity burden, which leads to an increasingly challenging kidney replacement therapy (KRT) journey. In the current era of patient-centric care model, patient's opinion on their care needs to be heard. They need to receive adequate and balanced discussion on the pros and cons of KRT and kidney supportive care. The primary care physician plays a crucial role to help establish the plan. The primary care physician, who has a long-standing rapport with their chronic disease patients and a deep knowledge of their multiple medical conditions, is most suitable to initiate advanced care planning (ACP) in the primary care setting. ACP is best done in a setting where the patient is well and comfortable with discussing this issue with someone the patient is comfortable with. By passing on this information to the referred nephrologist, it will help to bring the nephrologist up to speed on patient's opinion

and needs and assist in the planning of long-term kidney care plan.

CONCLUSION

A collaborative effort between the primary care physicians and nephrologists to manage the CKD progression and CKD complications is needed to optimise CKD care and guide CKD patients along their chronic disease journey.

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