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MAKING SENSE OF CHRONIC KIDNEY DISEASE IN PRIMARY CARE – IDENTIFICATION, EVALUATION AND MONITORING

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ABSTRACT

Primary care providers are often the first to diagnose chronic kidney disease (CKD). CKD progression is associated with significant morbidity, mortality and cost to the public healthcare system. Prompt and appropriate initial evaluation of CKD, recognition of its complications, and instituting appropriate treatment will delay CKD progression and associated adverse outcomes.

Keywords: Chronic kidney disease, diabetes mellitus

INTRODUCTION

Chronic kidney disease (CKD) is a major and escalating health problem. In 2017, 697.5 million cases of all-stages CKD were recorded worldwide, corresponding to a prevalence of 9.1 percent, an increase of 29.3 percent since 1990.[1] The prevalence of CKD in Singapore has risen over the last decade and now ranks fourth globally, largely contributed by the rising prevalence of diabetes, hypertension, and ageing.[2,3] Each stratum of CKD progression is associated with a two-fold increase in the risk for all-cause hospitalisation and mortality, leading to an increased annual incremental cost exceeding SGD $11,180 per capita in 2016.[4] This underscores the importance of primary care providers in identifying CKD early, delay CKD progression and its associated adverse outcomes. This article focuses on the diagnosis, evaluation and monitoring of CKD in primary care.

DEFINITION

The first definition of CKD was published in 2002 when the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) promulgated clinical practice guidelines.[5] The Kidney Disease: Improving Global Outcomes (KDIGO) conference in 2012 revised the classification to improve prognostication in CKD by including albuminuria. Information from 45 cohorts including more than 1.5 million people were pooled into a meta-analysis which found that estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73m^2 and higher urinary albumin-creatinine ratio (uACR) were associated with higher all-cause mortality, cardiovascular mortality, end-stage kidney disease (ESKD), acute kidney injury and progressive CKD.[6]

The KDIGO 2012 guideline defines CKD as abnormalities of kidney structure or function, present for >three months, in the form of either presence of markers of kidney damage (albuminuria ≥30 mg/24hrs, uACR ≥3 mg/mmol, urine sediment abnormalities, electrolyte or other abnormalities due to tubular disorders, abnormalities detected by histology, or structural abnormalities detected by imaging, or a history of kidney transplant), or decreased GFR < 60 mL/min per 1.73m^2. CKD is then staged into 18 categories based on GFR category (G1, G2, G3a, G3b, G4, G5) and albuminuria (A1, A2, A3) (Figure 1). This framework categorises patients into low, moderate, high and very high risk for CKD progression.[7] The discussion in this article will use this classification.

Glomerular filtration rate, an evaluation of kidney function, can be measured using urinary or plasma clearance of filtration markers such as inulin, iothalamate and iohexol. However, measured GFR (mGFR) is relatively expensive and not routinely obtained. GFR is estimated from standardised serum creatinine using the updated 4-variable Modification of Diet in Renal Disease (MDRD) Study, or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, both of which have been found to be sufficient for clinical decision making in the majority of the CKD population (with GFR < 60 mL/min per 1.73m^2), except in extremes of age, body habitus or diseases of skeletal muscle.[8] We demonstrated that the CKD-EPI equation is more accurate than the MDRD study equation throughout the GFR range in Asian patients of different ethnicities, and therefore recommend the CKD-EPI equation for practice, without adjusting for "Race" (treat all as "white").[9] The KDIGO 2012 CKD guideline recommends using the CKD-EPI creatinine equation for eGFR reporting.

Proteinuria is identified either by timed or spot urinary collections for measurements of albumin or protein concentrations. While a 24-hour urine collection for albumin and protein addresses issues of circadian protein secretion, it is less practical for routine clinical practice. Early morning spot urine albumin-creatinine ratio (uACR) and urine protein-creatinine ratio (uPCR) correlate with their 24-hour counterparts, are cost-effective and have

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a good predictive performance of CKD progression and ESKD.[10-12] As the sensitivity of uACR in identifying low levels of proteinuria is higher than that of uPCR, first void uACR collection (second void after waking up) is recommended for first-line screening in the KDIGO 2012 guidelines.[13] uPCR has been more accurate than uACR when estimating proteinuria of >1g/day and is considered acceptable for monitoring CKD when uACR is high (>500 to 1000mg/g).[14] uPCR is also used for monitoring treatment response in glomerulonephritis. When large discrepancies between uPCR and uACR, non-albumin proteinuria are seen, testing for monoclonal gammopathy (non-albuminuria proteinuria) is required.[7]

WHO AND HOW FREQUENTLY SHOULD WE SCREEN FOR CKD?

KDOQI recommends routine assessment for CKD with blood pressure monitoring, albuminuria, and serum creatinine in high-risk patients including those with diabetes, hypertension, autoimmune diseases, systemic infections, urinary tract pathology, neoplasia, family history of chronic kidney diseases, amongst others.[15] Guidelines on the evaluation of albuminuria and proteinuria in different countries vary.

A history of acute kidney injury, particularly that requiring dialysis, increases the cumulative lifetime risk for CKD and CKD progression. The Ministry of Health, Singapore (MOH) recommends annual screening for CKD with urinary albumin assessment and estimated GFR in patients with diabetes (five years after diagnosis of type 1 diabetes and at diagnosis in type 2 diabetics) and hypertensive patients but does not provide further guidance on other risk factors.[16,17] Given the high prevalence of CKD and risk factors for CKD, we recommend that CKD screening be performed in all at-risk populations according to the KDOQI guidelines.

CKD EVALUATION

Once the diagnosis is established, the evaluation of CKD is centred on distinguishing CKD of metabolic disease (namely diabetic kidney disease, hypertensive nephrosclerosis or secondary FSGS related to obesity) from that of other glomerular or genetic diseases. Evaluation in later stages of CKD focuses on screening for complications including volume excess, uraemia, mineral bone disease and anaemia.

Diabetic kidney disease is a spectrum of clinical presentations. Although guidelines described characteristics that indicate diabetic kidney disease, namely macroalbuminuria or microalbuminuria with diabetic retinopathy, or a diabetes duration extending more than ten years in Type 1 diabetics, the definitive diagnosis is through a kidney biopsy.[18] Patients with other kidney diseases will have different prognoses and therapies. Hypertensive nephrosclerosis is almost a diagnosis of exclusion, given its vague descriptive entity, and should be reserved for patients with proven stable renal function and low-grade proteinuria, without evidence suggestive of glomerular disease. Primary glomerulonephritis and diabetes or hypertension can coexist.[19,20] If a satisfactory cause of CKD is not identified, or glomerulonephritis is suspected, a kidney biopsy must be arranged.

Besides evaluating kidney disease, a holistic assessment affects decisions for Nephrology referrals. This includes evaluation of co-morbid conditions, frailty, age and physical performance, social and financial circumstances. Elderly, sick and frail patients with limited longevity will not benefit from enrolment into a complex artificial life support program. This would be burdensome or detrimental to the overall care of the patient. In fact, based on the National Disease Registry office data, only 50 percent of patients with ESKD due to diabetes survive five years.[2] Thus, primary care doctors emphasising conservative kidney care and subsequent palliation in uraemia may be the most appropriate management for many patients.

MONITORING FOR CKD PROGRESSION AND ITS COMPLICATIONS

Monitoring GFR and albuminuria at least once a year is recommended, and more frequently with decreasing GFR and increasing albuminuria. The frequency of monitoring is adjusted according to CKD stages and albuminuria categories (Figure 2).

In advanced stages of CKD (CKD stage G3 and above), patients develop increasing risks of complications of electrolyte disturbances, acidosis, anaemia, mineral bone disorder and cardiovascular disease.

Anaemia in CKD occurs due to decreased erythropoietin, a hormone mainly produced by the kidneys. Other mechanisms include uraemia-induced inhibitors of erythropoiesis and shortened red blood cell survival, and nutritional deficiencies.[21] Regular screening for anaemia is recommended from stage G3, with increasing frequency in later CKD stages (Table 1).[7] Workup of anaemia includes assessment for adequate iron, vitamin B12 and folate stores, and excluding bleeding (age-appropriate colon cancer screening). If haemoglobin concentrations remain persistently <10g/dL despite addressing reversible causes, consult a Nephrologist on possible initiation of injections of erythropoietin-stimulating agents.[22] Oral hypoxic-inducible factor (HIF) prolyl hydroxylase (PH) enzyme inhibitors have become available, with Health Science Authority regulatory approval expected in 2021, and this will likely change the way CKD-related anaemia is managed.

Table 1: Frequency of screening for anaemia in CKD

CKD Stage	Without anaemia	With anaemia not treated with Erythropoiesis Stimulating Agents
G3	Annually	At least every three months
G4-5 (non-dialysis)	At least twice a year	At least every three months
ESKD	Every three months	Peritoneal dialysis: every three months Haemodialysis: every month

Mineral and Bone Disorders (CKD-MBD) have complex pathophysiology in CKD and are associated with increased risks for fractures, vascular and tissue calcification, and mortality.[23] The KDIGO guidelines recommend monitoring for CKD-MBD complications from CKD G3a (Table 2).[7] Targets for treatment are controversial, as the bone biopsy is not available to guide treatment although it is widely accepted to correct serum calcium and phosphate concentrations within the normal reference ranges. Treatment options should be guided by a Nephrologist and include phosphate binders, activated Vitamin D analogues, calcimimetic agents and parathyroidectomy for tertiary hyperparathyroidism.[24]

Table 2: Frequency of screening for Mineral Bone Disease in CKD

CKD Stage	Serum calcium, phosphate, PTH	Alkaline phosphatase
G3	Serum calcium and phosphate every 6-12 months PTH: based on baseline level and CKD progression	
G4	Serum calcium and phosphate every 3-6 months PTH: every 6-12 months	ALP: every 12 months, or more frequently in presence of elevated PTH
G5 including ESKD	Serum calcium and phosphate every 1-3 months PTH every 3-6 months	ALP: every 12 months, or more frequently in presence of elevated PTH

Electrolyte and acid-base abnormalities: Management of hyperkalaemia allows optimal use of renin-angiotensin-aldosterone system blockers which are beneficial in retarding CKD progression and reducing cardiovascular deaths. Besides emphasising a low-potassium diet, prescribe diuretics for lowering blood pressure and increasing potassium excretion. Potassium lowering agents such as sodium polystyrene sulfonate or newer agents (sodium zirconium cyclosilicate, patiromer) are also treatment options. Metabolic acidosis (serum bicarbonate <22mmol/L) is associated with accelerated CKD progression and all-cause mortality.[25] Supplementation with oral sodium bicarbonate (500mg to 3g daily in divided doses) should be considered to achieve serum carbon dioxide of between 23 to 26 mmol/L.[22] Excessive sodium intake may worsen fluid overload or uncontrolled hypertension, and concomitant management of these conditions is required.

WHICH CKD PATIENTS DO WORSE?

Most patients with CKD do not end up requiring dialysis.[26] Risk stratification helps identify those at risk for CKD progression and ESKD, guide clinicians in deciding on the intervals between follow-up visits and planning for kidney replacement therapy. The Kidney Failure Risk Equation (KRFE) uses demographic and laboratory data to predict the risk of requiring dialysis or kidney transplantation in two and five years among individuals with GFR < 60mL/min per 1.73m^2.[27] The KRFE has been validated in various populations including Asian cohorts (*https://kidnefailurerisk.com/)*. The 4-variable equation incorporates age, sex, eGFR and uACR. The 8-variable equation includes serum albumin, phosphate, calcium and bicarbonate concentrations. The KFRE provides risk thresholds for referral to a nephrologist. A trial aimed at determining if KRFE risk-based approach improves CKD management in the primary care pathways is in progress.[28]

Rapid progression is defined as a sustained declined in eGFR of > 5 mL/min/1.73m^2 per year. These patients are at an increased risk of rapid progression to ESKD and also an increased risk of death and vascular disease-related events[7] and will benefit from consulting a Nephrologist.

There are patients with slowly progressive (stable) CKD (GFR decline < 1 mL/min/1.73m^2 per year).[29] These tend to be elderly patients who fulfil the criteria for CKD solely due to eGFR criteria. Some nephrologists believe that these are expected age-related changes and such patients should not be considered to have CKD.[30] Physiological decline in GFR occurs after the age of 35-40 years due to progressive nephron loss from focal and global glomerulosclerosis preferentially affecting the superficial cortex, unaccompanied by the compensatory glomerular enlargement or hyperfiltration in the remaining glomeruli. This is in contrast to nephron loss in early CKD which is diffuse across the cortical depth and associated with glomerular enlargement in residual nephrons. In addition, epidemiological studies have found that in individuals older than 65 years, mortality risk increases only when eGFR < 45 mL/min per 1.73m^2 when compared to that of a reference group of similarly aged persons with eGFR 75-89 mL/min per 1.73m^2. In younger persons, however, increased mortality risk is observed beginning from eGFR < 75mL/min per 1.73m^2 when compared to a reference of eGFR ≥105 mL/min per 1.73m^2.[30]

WHEN TO CONSULT NEPHROLOGY?

Many patients with CKD are managed by primary care physicians. In later stages of the disease, timely referrals to a Nephrologist allow for management of CKD complications and for a transition to ESKD care. The options include conservative kidney care or enrolment into artificial life support programs such as kidney transplantation or kidney replacement therapy with peritoneal dialysis (initially), then haemodialysis. Guidelines recommend consulting a Nephrologist when eGFR is < 30 mL/min per 1.73m^2 (stage G4) or when uACR increases above 30 mg/mmol (stage A3) or uPCR of 50 mg/mmol or more. We showed earlier nephrology management in CKD to ESKD transition is associated with better patient outcomes and reduced mortality.[31]

All suitable patients with kidney disease should undergo a kidney biopsy for a definitive diagnosis. Proper identification, classification, and prognostication of CKD allow patient-centric care. Patients with acute kidney injury or abrupt sustained fall in GFR, CKD progression (drop in GFR category accompanied by a 25 percent or greater drop in eGFR from baseline, or rapid GFR progression) (no associated medical treatment changes) and urinary red cell casts or sustained and unexplained RBC >20 per high power field must be assessed by a Nephrologist. These patients may require a kidney biopsy for evaluation for glomerulonephritis or interstitial diseases.[32] Other indications include CKD and hypertension refractory to treatment with four or more antihypertensive agents, persistent abnormalities of serum potassium, recurrent or extensive nephrolithiasis or hereditary kidney disease.[7]

The Holistic Approach in Lower and Tracking Chronic Kidney Disease (HALT-CKD) Programme was implemented in 2017 in all public primary care clinics (polyclinics). A set of interventions aimed to optimise CKD care and prevent progression to ESKD and recommends a referral to the Nephrologist at an eGFR < 45 mL/min per 1.73m^2 (Stage G3b).[33] The eGFR threshold is an artificial cut-off as it does not account for the expected trajectory of CKD progression. Trajectories of eGFR decline are highly variable and depend on albuminuria, age, and risk factor control. Patients who are rapid progressors require early Nephrology review, whereas the non-progressors may never reach ESKD. Nonetheless, specialist review of moderately severe and severe CKD will increase definitive diagnoses, optimise medical management, and improve patient health literacy on treatment options including avoiding unnecessary dialysis initiation and pursuing early decisions on conservative kidney care.

CONCLUSION

Chronic kidney disease is common and a global health problem. CKD screening, evaluation, monitoring and timely referrals to the Nephrology service are crucial in improving patient outcomes.

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LEARNING POINTS

- **All estimated GFR equations have inherent bias and inaccuracies, but the CKD-EPI equation is preferred in the local context for assessing estimated GFR.**
- **Non-diabetic nephropathies occur in a significant number of diabetic patients with CKD. A native kidney biopsy remains the gold standard to elucidate and can dramatically alter a patient's kidney disease trajectory and renal prognosis.**
- **Although CKD 3B (estimated GFR < 45 mL/min per 1.73 m^2) has been made an empirical cut-off for referral to Nephrology, young patients, those who have proven to be rapid progressors (estimated GFR decline > 5 mL/min per 1.73 m^2) and those with suspicion for glomerulonephritis need to be referred early.**
- **In contrast, many elderly patients with CKD 3B by estimated GFR criteria may be non- or slow progressors, and chronic follow-up in these patients are probably better served in primary care.**

Figure 1: KDIGO 2012 Classification of CKD

				Persistent albuminuria categories		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30mg/g <3mg/mmol	30-300mg/g 3-30mg/mmol	>300mg/g >30mg/mmol
GFR categories (mL/min per 1.73m²)	**G1**	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low-risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high-risk; red: very high-risk

Figure 2: KDIGO 2012 Guide to frequency of monitoring by GFR and albuminuria category

				Persistent albuminuria categories		
				A1	A2	A3
Guide to frequency of monitoring (number of times per year) by GFR and albuminuria category				Normal to mildly increased	Moderately increased	Severely increased
				<30mg/g <3mg/mmol	30-300mg/g 3-30mg/mmol	>300mg/g >30mg/mmol
GFR categories (mL/min per 1.73m²)	**G1**	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60-89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45-59	1	2	3
	G3b	Moderately to severely decreased	30-44	3	3	3
	G4	Severely decreased	15-29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

GFR and albuminuria grid to reflect the risk of progression by intensity of colouring (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year).