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AN APPROACH TO CHRONIC KIDNEY DISEASE IN THE ELDERLY – USE OF THE KIDNEY FAILURE RISK EQUATION

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Abstract

Chronic kidney disease (CKD) in the elderly population is very common; however, it is important to distinguish physiologic decline in Glomerular Filtration Rate (GFR) from a clinically significant disease that leads to dialysis dependence and increased mortality and morbidity. Despite having low GFR, many elderly patients do not progress to end stage kidney disease. The use of prognostic tools allows for individualized care and identifies high-risk individuals needing higher intensity of nephrology involvement. Furthermore, there is a lack of CKD guidelines specific to elderly populations, making management challenging. Cardiovascular risk factor optimization is important for maintaining renal health, but geriatric specific concepts, such as frailty, need to be incorporated into care plans. For patients with advanced chronic kidney disease, decisions regarding renal replacement therapy requires a multidisciplinary approach with a focus towards patient education and goals of care discussions.

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Cardiovascular Disease, Frailty, Hypertension, Polypharmacy, Renal Disease

Introduction

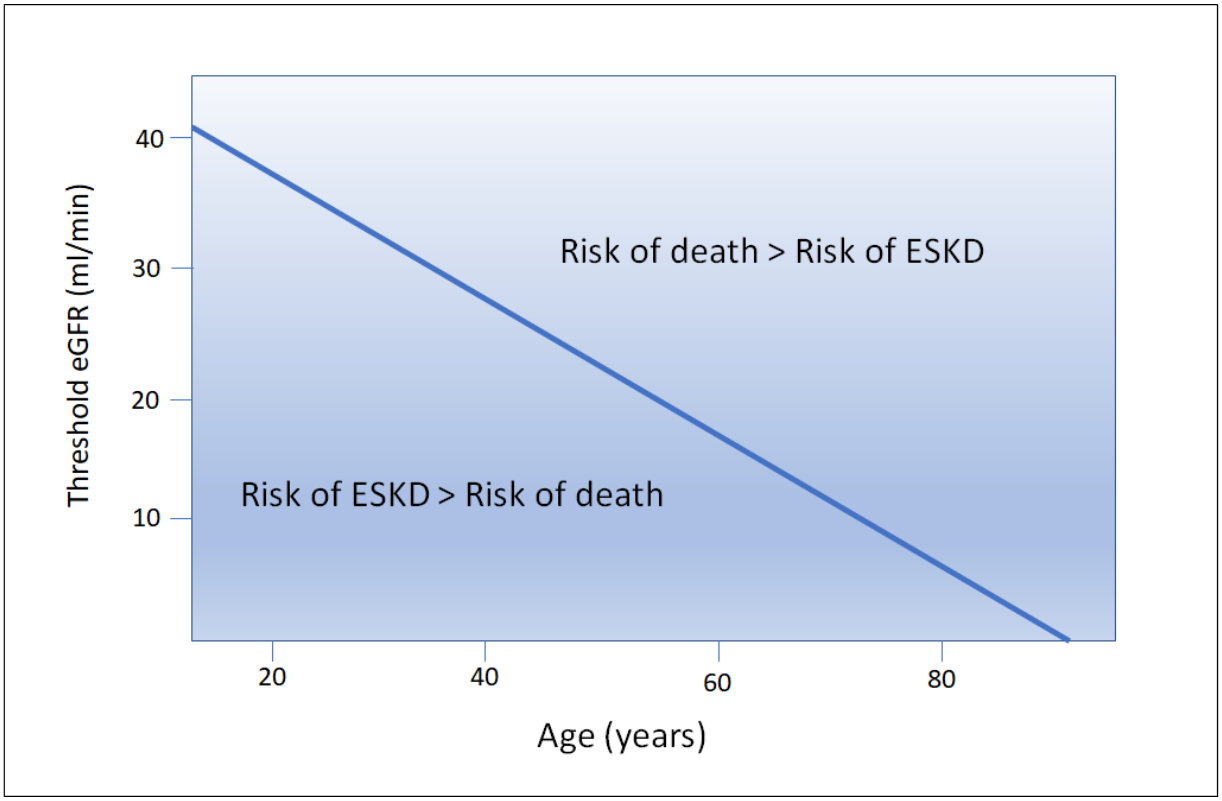
Chronic kidney disease (CKD) in elderly populations is a burgeoning concern; it has been described as a worldwide epidemic with significant morbidity and health care resource utilization[1]. CKD management in the elderly is complicated by a paucity of evidence-based guidelines; h ealth care providers should be cognizant of the pitfalls of extrapolating from guidelines developed for the general population to older patients. This review aims to explore the causes and consequences of reduced kidney function in elderly patients, and outlines evidence-based practices in geriatric nephrology.

Physiology of CKD in elderly

The effects of reduced estimated Glomerular Filtration Rate (eGFR) in elderly patients are complex; individuals with elevated creatinine are not always destined for end stage kidney disease (ESKD). There is a physiological decline in GFR starting in the third and fourth decade of life with an approximate 8ml/minute loss every decade [2]. Age related GFR decline is due to renal cells entering senescence or cellular apoptosis [3]. The process is accentuated by inflammation from co-morbid diseases [4]; arteriosclerosis develops with subsequent ischemia resulting in the upregulation of molecular pathways that promote cellular senescence leading to the development of interstitial fibrosis and atrophy of renal tubules. A hallmark of age-related renal decline is the relative absence of proteinuria [5], which portends a favourable prognosis[3]. In contrast, systemic inflammatory and atherosclerotic diseases are associated with the development of extensive glomerulosclerosis and interstitial fibrosis and atrophy, resulting in an accelerated decline in nephron number and development of albuminuria[3]. Factors that are linked to accelerating the age-related decline include hypertension, hyperglycemia, atherosclerotic cardiovascular disease, smoking, hyperlipidemia and previous episodes of acute kidney injury [6].

It is thus important to identify patients that are at higher risk of progressing to advanced stages of kidney disease. Such patients require more intense control of their risk factors. CKD stage (I – V) based on eGFR alone is not an ideal discriminant. Creatinine based eGFR using the CKD-epi model has several drawbacks, and can be affected by age, sex, ethnicity and muscle mass [7]. The rate of eGFR decline may be more informative to clinicians; patients with a slow eGFR decline (less than 2ml/min/year) may never reach ESKD as death from other causes becomes a significant competing factor (Figure 1) [8]. Estimated GFR, in combination with albuminuria, does have prognostic utility. Tangri *et al* developed the Kidney Failure Risk Equation - KFRE (https://kidneyfailurerisk.com), which predicts a 2- and 5- year risk of ESKD based on age, gender, eGFR and albumin creatinine ratio. Individuals with a 5- year KFRE score of greater than 5% warrant a referral to a nephrologist [9].

Figure 1. There is a competing risk of death and ESKD that varies with age. The likelihood of progressing to ESKD from any particular baseline eGFR attenuates with age. Adapted from Shim, R.L. and O'Hare, A. M., 2006 [8].



Managing cardiovascular risk factors

Blood pressure (BP), lipid, and glycemic control are the cornerstones of kidney disease management [6]. Patients with poorly controlled cardiovascular risk factors are at much higher risk of progressive renal decline [10]. There is also ample evidence that low blood pressure and albuminuria reduction are reno-protective; Renin Aldosterone Angiotensin System (RAAS) blockade is crucial to achieving these ends [11]. Hypertension Canada recommends a target BP goal of less than 130/80mmHg in patients with DM, less than 120/80 in patients without DM [12]. These recommendations were primarily based on the SPRINT trial, a multi-center randomized control trial examining blood pressure goals of <120mmHg versus <140mmHg with outcomes significant for improved survival and fewer cardiovascular events in the intensive treatment arm [13]. The Kidney Disease: Improving Global Outcomes (KDIGO) 2021 guidelines recommended intensive BP lowering in all patients, irrespective of diabetes status [14]. One must exercise caution in older patients. Hypertension Canada and KDIGO both acknowledge the limitations of evidence for BP lowering in older patients [12,14]. Studies such as HYVET and AASK incontrovertibly demonstrate the importance of BP control, but patients with significant frailty with risk of falls may require restraint in lowering BP [15,16]. One must consider the possibility of postural hypotension (see www.posturalhypotension.com) and routinely measure BP supine vs. standing. If postural hypotension is present, additional contributors for modification from Table 1 in 4D-AID-A-Practical-Approach-to-the-Assessment-of-Orthostatic.pdf (canadiangeriatrics.ca) can be addressed and other treatments (see TREATMENT-OF-ORTHOSTATIC-HYPOTENSION-IN-OLDER-PATIENTS.pdf (canadiangeriatrics.ca)) can be considered. If the patient is deemed to be frail and/or postural hypotension is an issue creating risk for falls then less tight BP targets may be considered (see Table 2 in Can-We-Stay-on-Target-A-Review-of-Hypertension-Treatment-in-the-Elderly.pdf (canadiangeriatrics.ca))

Polypharmacy is also a major issue; it predisposes a risk of falls, electrolyte abnormalities and AKI, especially with diuretics. A post hoc analysis of the SPRINT trial showed a higher risk of adverse events in patients with lower diastolic BP [17], a common occurrence in elderly populations. Thus, an individualized approach is best in older patients that are frail or institutionalized.

Similarly, glycemic control needs to be modulated according to patients' individualized needs. The Diabetes Canada guidelines recommends that HbA1c targets should be dependent on frailty: aiming for HbA1c 7.1% - 8.5% in patients with dementia is a reasonable strategy, with a focus towards avoiding extremes in blood sugars. For most other elderly patients, the target should be HbA1c 7.0 – 8.0% [18]. For more information see Layout 1 (canadiangeriatrics.ca) .

Hyperlipidemia management in older patients reduces cardiovascular events and mortality; however, this effect is attenuated or even lost in the very old (age > 85) [19]. Lowered dosing should be considered in elderly patients with CKD, and patients should be monitored for myopathies [20]. Given the potential muscle side-effects off statins, it may be prudent to defer statin therapy in frail patients with poor nutrition and appetite who are already at risk of sarcopenia [19].

Anemia management in CKD

Anemia of chronic kidney disease is very common and is often related to relative erythropoietin deficiency [21]. Older adults may have pre-existing anemia secondary to malignancy, chronic inflammation or nutritional anemia [22]. Symptoms of anemia such as fatigue, decreased exercise tolerance and cognitive dysfunction may be magnified in elderly patients and deleteriously impact quality of life [23]. Furthermore, anemia in the CKD population is associated with increased cardiovascular events, hospitalizations, transfusions and death [24]. Iron deficiency anemia is also common in CKD patients, and requires nuanced interpretation of ferritin, and transferrin saturation [25]. Ferritin levels are often elevated in CKD patients and do not rule out iron deficiency [26]. KDIGO recommends a trial of IV iron for patients with TSAT <30% and ferritin <500ng/ml, despite oral supplementation [27]. Per Canadian Society of Nephrology guidelines, an erythropoeitin stimulating Agent (ESA) should be initiated when the hemoglobin (Hgb) level is between 90-100g/L with a target range of 100-110g/L [28]. Patients require concomitant treatment with EPO and iron, as patients with inadequate iron stores will be hyporesponsive to EPO therapy and will require higher doses of ESA's. Higher Hgb levels in patients on ESA's are associated with increased mortality, cardiovascular outcomes, thrombosis, and stroke [29]. Higher Hgb levels may be targeted in older palliative patients with severe fatigue symptoms but attempts at normalizing Hgb (>130g/L) should be strictly avoided [30].

Osteoporosis/ Bone Health and CKD

Bone health is a crucial consideration in any elderly population, and particularly so in patients with CKD, where there are significant derangements in the calcium-phosphate balance. Studies have shown a 4.4 greater risk of fragility fractures in CKD stage V [31]. CKD related mineral bone disease not only increases the risk of fragility fractures, it is also associated with poor muscle function, systemic calcification and consequent vascular disease [32]. Traditional diagnostic tests such as bone densitometry scans (DEXA) can be difficult to interpret in CKD, however, newer guidelines recommend the use of DEXA scans to follow treatment effects [33]. Bone biopsies are the gold standard but are not routinely recommended due to their invasive nature [33]. For more information see Volume 5, Issue 2 – Common Controversies in Osteoporosis Therapy – The Canadian Geriatrics Society .

Treatment of hypocalcemia and hyperphosphatemia (defined as PO_4 > 1.5mmol/L) with diet control and phosphate binding medications optimizes bone health, as does usage of 25-OH vitamin D formulations [34]. As CKD progresses, the ability to hydroxylase 25 OH vitamin D to 1,25-OH vitamin D3 wanes, and supplementation with calcitriol is required [35]. Calcimimetics (Calcium Sensing receptor antagonists), such as cinacalcet, treat secondary and tertiary hyperparathyroidism and reduce fracture risk [36], and may be particularly beneficial in elderly patients [37]. These medications serve as a viable alternative to surgical parathyroidectomy. Phosphate control is controversial in older patients. Limiting protein intake can lead to poorer nutrition, and

worsened frailty [38]. Phosphate binders (e.g., calcium carbonate) may allow for liberalization of diet. Excessive use of calcium-based phosphate binders may lead to increased calcium deposition within blood vessels and hypercalcemia [33]. Non calcium-based binders such as sevelamer or lanthanum salts are alternative options but are not covered by public health plans routinely. Aluminum based salts were very effective, but lead to aluminum toxicity in CKD patients, and are contraindicated [33].

Treatment of osteoporosis is made challenging in the renal population due to the relative contraindication of traditional anti-resorptive medications like bisphosphonates, and denosumab, a RANKL inhibitor. Recent evidence shows that bisphosphonates may be effective in slowing bone density loss [39]. Bisphosphonates can potentially worsen renal function by causing acute tubular necrosis, as well as collapsing FSGS, but these are relatively rare side-effects, and dose adjustments may mitigate harm [40]. High levels of bisphosphonates may predispose patients to osteonecrosis, or adynamic bone disease [41]. Lowering doses and increasing the dosing interval is recommended if these drugs are to be used. It is worth noting that most cases of bisphosphonate nephrotoxicity were in the context of intravenous bisphosphonates e.g., zolindronic acid [39]. Denosomab may be a reasonable alternative, but clinicians need to monitor for hypocalcemia [42]. The evidence for therapeutics such as is raloxifene and terapeptide is less clear [42]. For more information see Volume 5, Issue 2 – Common Controversies in Osteoporosis Therapy – The Canadian Geriatrics Society.

Metabolic acidosis

As renal function declines, there is an increased loss of bicarbonate and decreased renal excretion of acids resulting in the development of metabolic acidosis [43]. Chronic metabolic acidosis may contribute to osteopenia, muscle catabolism and systemic inflammation all of which are exacerbated in the elderly [44]. Furthermore, there is an association with increased mortality seen in observation studies in patients with bicarbonate levels <22mEq/L in addition to an increased risk of progression of CKD [44]. As such, KDIGO recommends initiating treatment with oral bicarbonate when serum levels are <22mEq/L [43].

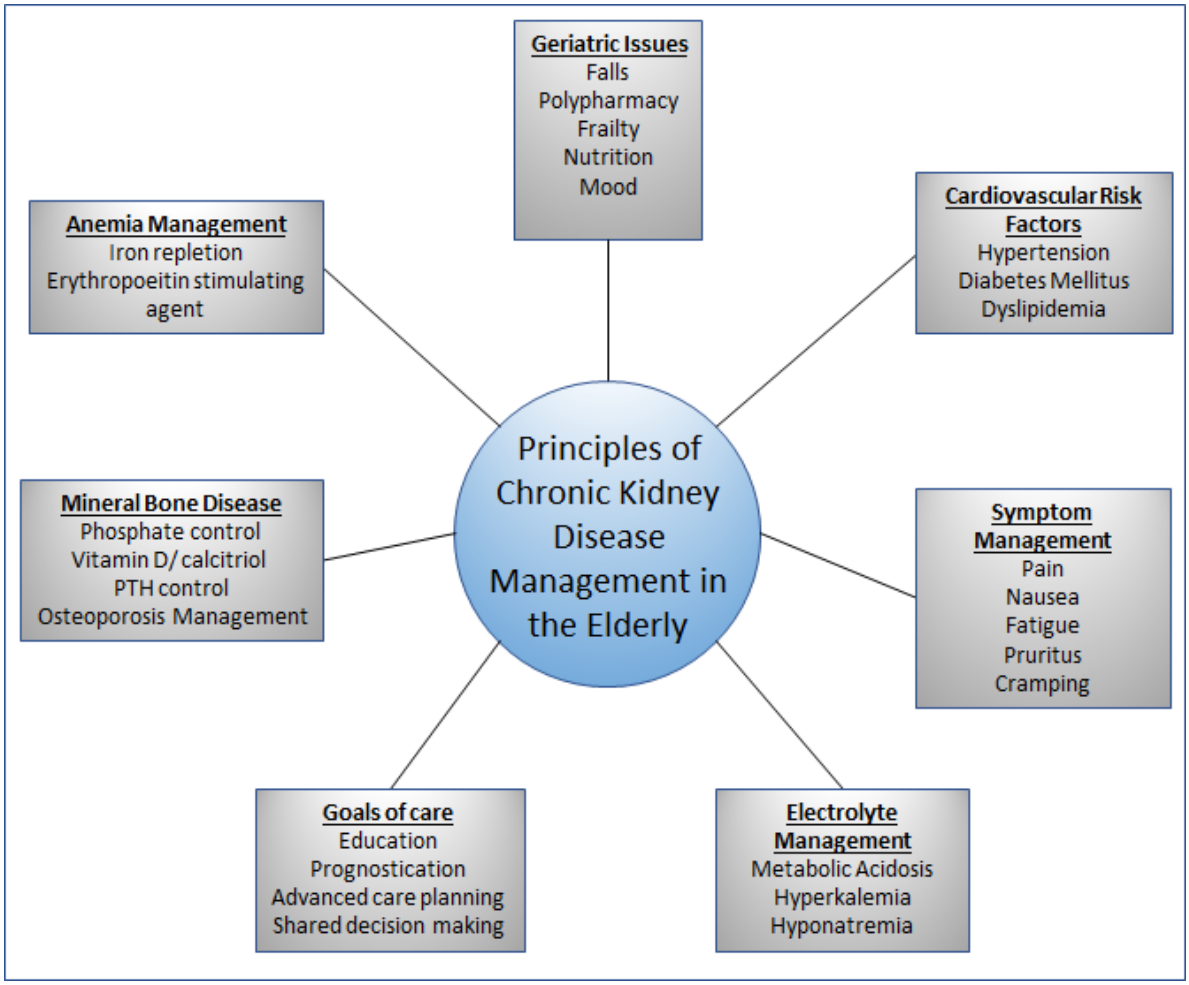
Goals of care planning

As renal function declines, it becomes imperative to discuss future planning and elicit goals of care as they pertain to end stage kidney disease and renal replacement therapy. It is important for the patient and their family to understand the potential benefits and harms of renal replacement therapy while incorporating their values and preferences in a shared decision-making process [45]. This is associated with less decisional regret, and increased satisfaction with their care [46]. Resources such as the Serious Illness Conversation Guide from Ariana Labs (https://www.ariadnelabs.org/wp-content/uploads/2017/05/SI-CG-2017-04-21_FINAL.pdf) can be very helpful. The Ontario Renal Network provides resources for nephrology teams and faculty development seminars as well to help improve communication skills for advanced care planning (https://www.ontariorenalnetwork.ca/en/kidney-care-resources/clinical-tools/palliative-care).

Patients with ESKD may experience symptoms related to the accumulation of uremic toxins, including fatigue, loss of energy, decreased appetite, metallic taste in addition to shortness of breath/lower extremity edema, and poor cognition [47]. While dialysis may provide increased survival and symptom relief, this benefit is often very modest in older and frailer patients [48], with a significant reduction in quality of life, and independence as a trade-off [49,50]. In Canada, for patients older than 70, the 1-year survival is 76% with a 5-year survival of 28% [51]. Elderly patients undergoing dialysis experience significant symptom burden with an average of 5-6 symptoms, with the predominant symptom being fatigue [52]. This fatigue is often multi-factorial; however, dialysis itself can contribute and worsen fatigue (post-dialysis fatigue) [53]. Time to recover from post-dialysis fatigue can vary from minutes to hours [54]. Other symptoms include pain, muscle cramps, difficulty with sleep and sexual dysfunction [52]. Patients who have a higher symptom burden often have reduced functional status, and decreased mobility resulting in diminished quality of life. As many as 25% of patients on hemodialysis suffer from depression in addition to the symptoms above [55]. A high symptom burden has been associated with increased risk of hospitalization, institutionalization, and mortality. Home-based modalities such as peritoneal dialysis may be better tolerated in patients and can be provided with the help of home care nurses [56].

Conservative renal care without dialysis may be a viable option in patients with significant co-morbidities and high degree of frailty. The focus is on palliating symptoms and avoiding invasive discomforting therapies that only provide a small incremental benefit in survival [57]. A key aspect in ensuring successful palliation is developing partnerships with palliative care services that can help transition patients to the end of life as uremia worsens.

Figure 2. Principles of CKD Management in the Elderly.



Conclusion and future directions

CKD in the elderly population is very common and is associated with significant morbidity. A patient-centered approach is warranted to balance the benefits of reno-and cardiovascular optimization with the risks of adverse events and polypharmacy. Patients at higher risk of advanced progressive kidney disease should be managed in a multi-care kidney clinic by a team that includes nurses, pharmacists, dieticians social workers and physicians. Management of our elderly patients must incorporate geriatric competencies such as recognizing frailty, cognitive impairment and the impacts of polypharmacy. Various tools such as the clinical frailty scale can be useful to identify patients at high risk for functional decline, however they have reduced sensitivity to identify frailty in busy renal clinics [58]. Geriatric clinics can be a valuable resource for nephrologists by performing comprehensive geriatric assessments [58], thereby identifying and managing patients at high risk of geriatric syndromes and assessing patients socio-economic and environmental needs [59]. Fostering partnerships with geriatric and palliative colleagues would be instrumental in establishing a more nuanced and holistic approach to care of the elderly and ensure that their goals and values are respected and incorporated into

their management plans. We should endeavour Multiprofessional and interdisciplinary educational rounds would allow the two specialties to learn from each other and develop comfort and expertise in CKD care in the elderly[59].

Key Points

Age related decline in renal function is physiologic and expected in older adults and the likelihood of progressing to ESKD from any baseline eGFR attenuates with age.

Estimated GFR alone does not accurately predict progression of renal disease and use of the kidney failure risk equation (KFRE (https://kidneyfailurerisk.com) may help providers stratify risk of CKD progression in patients.

Patients who have a KFRE risk of >5% over 5 years may benefit from a referral to Nephrology.

The management of risk factors for chronic kidney disease needs to be individualized and balanced between the patient's frailty and co-morbid conditions.

Dialysis may not be suitable for all patients, and a thorough patient centered discussion should be performed with consideration for potential benefits and harms to the patient.

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