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Chronic kidney disease in older adults: challenges and opportunities for the primary care provider

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Abstract

Kidney disease and its comorbidities disproportionately affect older persons. Kidney disease modifying therapy is underutilized in older adults, as guidelines lack consensus on approaching diagnosis and treatment in older adults. This review aims to highlight the challenges presented by, and opportunities for, identifying and treating CKD in older adults.

Keywords Chronic kidney disease (CKD), Primary care, Older adults

Background

Chronic kidney disease (CKD) in older adults presents unique challenges to primary care providers related to diagnosis, appropriate referral, and treatment considerations. When considering diagnosis, primary providers must balance the stress patients experience when diagnosed with CKD, the burden of visiting additional care providers, and utilization of limited healthcare resources against the risk of kidney disease progression and development of complications related to advanced CKD and end-stage kidney disease (ESKD). Further confounding this decision-making process is the idea that biologic age-related kidney function loss must be distinguished from pathologic causes of CKD [1]. Providers are tasked with balancing referring patients to nephrology early enough to afford patients opportunities for kidney protective therapy and focused nephrology care against the risk of referring patients who may never experience disease progression or associated complications. Without clear consensus from the US Preventive Services Task Force and or clinical practice guidelines about whether/how to identify patients at high risk of CKD progression, primary providers have faced this complex decision with limited guidance.

Emerging data on several agents shown to attenuate progression of diabetic and in some cases non-diabetic kidney disease and reduce associated cardiovascular complications necessitate a closer examination into how older adults with CKD are identified, prioritized for nephrology referral, and evaluated for kidney life-extending therapies. For three decades, nephrologists and primary providers alike relied on renin-angiotensin-aldosterone system (RAAS) antagonists as the only available therapy demonstrated to slow CKD progression, understandably discouraging nephrologists in their ability to favorably alter the trajectory of disease perhaps most notably in older adults where competing risks of frailty, major cardiovascular events, and death are most prominent [2–4]. Entering a new CKD treatment era coinciding with more patients aging well into their eighth, ninth

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and tenth decades, and available CKD therapies showing benefit in early disease, calls for a re-examination of the traditional CKD treatment paradigm. Strengthening partnerships between nephrology and primary care to support primary providers' treatment of early stage CKD care, could amplify the population effect of newer therapies and extend their longitudinal benefits to patients with kidney disease [5, 6].

Diagnosing CKD in older adults

Chronic kidney disease is defined by both measures of glomerular filtration rate (GFR) and albuminuria (often described interchangeably with proteinuria), sustained over a multi-month time span to establish chronicity. The GFR categorizes patients into one of six CKD "G stages" (and the urine albumin to creatinine ratio (UACR) categorizes patients into one of three "A" stages), determines a patient's place on the CKD spectrum vis-a vis likelihood of progression to kidney failure and guides treatment considerations [7]. The GFR ranges are age agnostic and thus the treatment guidelines for each GFR range apply to persons of all age groups. Some have argued that defining CKD stage using the same GFR ranges across the age spectrum does not adequately consider the minimal morbidity and mortality risk associated with GFR just below 60 mL/min in the older adult population and that by designating all older adults with an estimated GFR (eGFR) 45 to less than 60 mL/min/1.73m^2 as CKD Stage G3a, providers risk misclassifying age-related loss of kidney function as pathologic disease. Delanaye and colleagues have referred to this misclassification as "medicalizing senescence" [1]. Indeed, while not true for all older adults, there is compelling evidence to suggest that older persons generally experience slower rates of CKD progression than younger adults [8].

The presence and severity of frailty should be considered when evaluating kidney function in older adults. The serum creatinine – a by-product of muscle metabolism – is the most commonly used marker of the efficiency of solute (waste) removal. The eGFR is typically determined using a population regression equation incorporating the serum creatinine, age, and sex, recognizing that on average older persons and women typically have lesser muscle mass than younger persons and men [9]. Older adults with sarcopenia manifest lower than expected serum creatinine concentrations at a given level of kidney function (and in turn, higher eGFR); thus, older adults with frailty will often appear to have less severe CKD, or CKD will be masked entirely [10]. Confounding by body composition should be considered when evaluating the serum creatinine concentration and eGFR in frail older persons. Alternatively, eGFR may be calculated using serum cystatin C, concentrations which are not dependent on muscle mass and creatinine generation [11].

When considering diagnosing CKD in the older adult population, it is helpful to consider complications frequently seen with early and moderate stages of the disease. Chronic kidney disease is strongly associated with cardiovascular morbidity and mortality and the association strengthens with lower eGFR and more severe degrees of albuminuria/proteinuria [12]. While many providers obtain regular serum urea nitrogen and creatinine concentrations through commonly ordered metabolic panels, the risk of cardiovascular disease associated with CKD is largely driven by one's degree of albuminuria, rather than eGFR [13]. Screening for albuminuria not only helps to differentiate pathologic glomerular disease from physiologic age-related loss of kidney function, it also risk stratifies patients most in need of nephrology evaluation and kidney protective therapy. Several guideline writing bodies and kidney disease-focused advocacy societies agree that targeting CKD screening to those at highest risk of developing the disease (i.e. those with type 2 diabetes mellitus and hypertension) strikes a reasonable balance between diagnostic accuracy and resource utilization [14, 15]. Additionally, as payers are increasingly tying providers' reimbursement to meeting quality metrics, national bodies focused on care quality have recommended screening all patients aged 18–85 with diabetes with an annual GFR and UACR [16]. Despite these guidelines and the well-established risks of cardiovascular events associated with albuminuria/proteinuria, albuminuria screening rates among persons with diabetes across the US remain stagnantly low [17]. Historically, enthusiasm for population-wide screening for CKD has been hindered by a paucity of effective therapies to treat kidney disease once identified; in the coming years, groups including the US Preventive Services Task Force will re-evaluate the potential benefits and challenges associated with more comprehensive screening initiatives [18].

Opportunities to slow kidney disease progression

For nearly thirty years, the only agents available to attenuate progression of kidney disease were inhibitors of the renin-angiotensin aldosterone system, namely angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). While several studies explored the combination of drugs of both classes, there did not appear to be net benefit, and risks, including those of hyperkalemia, hypotension, and abruptly impaired kidney function, were more frequent and/or severe [19–21]. Among patients with CKD and type 2 diabetes, sodium-glucose transporter type 2 (SGLT2) inhibitors, finerenone, a non-steroidal mineralocorticoid receptor antagonist, and glucagon-like-peptide-1 (GLP1) receptor agonists have substantially broadened the repertoire of agents available to slow CKD progression [22–26]. The

advent of these potent therapies affects the calculus primary providers face when screening for, and considering treatment for, CKD in patients with diabetes across the age spectrum, including the older adult population [27, 28]. While CKD modifying benefits of finerenone and the GLP1 receptor agonists have been demonstrated in the diabetic population alone, the SGLT2 inhibitors dapagliflozin and empagliflozin have demonstrated potent protective effects in both diabetic and non-diabetic CKD populations [22, 24]. Expanded treatment options allow for more opportunity to reduce CKD-related morbidity and mortality and perhaps prevent an older adult patient from developing ESKD, as well as reduce older persons' risk of cardiovascular morbidity and mortality. With patients living more functional lives into their ninth and tenth decades, it has become increasingly important that primary providers address with those at risk of CKD progression the opportunity to forestall the development of kidney failure by initiating treatment for their kidney disease early in the disease course [6].

There is substantial evidence to support the benefit of SGLT2 inhibitors in older adults. Recently, Yu et al. showed in a pre-specified analysis of data from the DAPA-CKD trial that dapagliflozin reduced the risk of CKD progression, hospitalization for heart failure or cardiovascular death, and all-cause mortality in women and men across all age groups, including persons in their seventh and eighth decades who comprised 25% of the trial population [29]. This work aligned with findings from earlier cardiovascular outcome trials for SGLT2 inhibitors which showed broadly, and in subsequent post-trial analyses, that the efficacy and safety of SGLT2 inhibitors did not vary across age groups in patients with type 2 diabetes mellitus, heart failure with preserved ejection fraction, and heart failure with reduced ejection fraction [30–33]. Importantly, data from DAPA-CKD also showed that while older patients experienced more serious adverse events, the rates of these events were similar in patients treated with dapagliflozin and placebo [22]. The advent of the SGLT2 inhibitors, and their demonstrated efficacy and safety in elderly patients, changes the treatment landscape for primary care providers caring for patients with mild to moderate CKD and cardiovascular disease. Not only do these therapies afford patients the opportunity to slow CKD progression as they age, they confer significant protection against cardiovascular events, and in particular, heart failure, both feared complications of advanced age.

Despite the demonstrated opportunity for early intervention, evidence suggests lower usage of clinically indicated therapeutics among older when compared to younger individuals [34, 35]. Congruent with data demonstrating under usage of indicated cardiovascular medications in older adults when compared to younger counterparts with the same diagnosed conditions, data suggest a similar discrepancy when evaluating prescribing patterns for CKD-directed therapies. Older age has been associated with lower rates of RAAS inhibitor prescriptions in patients with non-dialysis dependent CKD. Correspondingly, more recent studies have demonstrated lower SGLT2 inhibitor usage in older versus younger patients, with one study demonstrating that the odds of prescribing an SGLT2 inhibitor were approximately 4% lower with each additional year of age in a population of 170,000 US veterans with type 2 diabetes and CKD or cardiovascular disease [36–38]. Primary care physicians have cited age as a significant factor influencing the decision to prescribe or not prescribe SGLT2 inhibitors to older adults, highlighting the concern for adverse drug effects and polypharmacy [39]. Prohibitively high medication costs have been identified as another common barrier to prescribing, often a more acute concern in the elderly population who are more likely to be living on a fixed income [40]. This prescribing pattern discrepancy across the age spectrum presents an opportunity for nephrologists to strengthen their specialty's partnership with primary care physicians, guiding physicians and non-physician primary care providers to intervene earlier in the course of CKD. While the beneficial effects of RAAS inhibitors in elderly persons with hypertension and CKD are well recognized, data supporting the use of SGLT2 inhibitors, finerenone, and GLP-1 receptor agonists may not be as familiar to providers outside of nephrology. This may also present an opportunity for health systems to leverage technology based decision support tools developed in collaboration between primary care and nephrology.

Opportunities to improve overall health

While the pharmacologic treatments available to slow CKD progression have expanded substantially over the last decade, discussion of healthy lifestyle habits, shown to improve overall health, is equally important in the older population. Most nephrologists agree that as part of general health discussion topics such as smoking cessation, maintenance of a healthy body weight, the benefits of aerobic and resistance exercise, and avoiding nephrotoxic agents should precede or at least accompany discussion about medications. Outside of data suggesting that moderation of dietary protein intake may slow CKD progression, there is a lack of compelling evidence that other lifestyle interventions effectively slow CKD progression or reduce the risk of kidney failure [41]. A discussion of general nutrition, blood pressure control, and physical activity helps both engage patients in their own care, and helps providers weigh the risks and benefits of polypharmacy. In considering a holistic approach to treatment however, the focus on CKD therapies must be set within

the context of older adults' overall health where general health topics take primary focus.

A practical approach

As more patients live more functional lives into their eighth, ninth and tenth decades, understanding how to approach the diagnosis and treatment of CKD in the elderly population offers a significant opportunity to improve care delivery through slowing CKD progression, sparing older patients from developing ESKD, and reducing cardiovascular morbidity and mortality. With substantial evidence demonstrating benefits of SGLT2 inhibitors in diabetic and non-diabetic kidney disease, and finerenone and semaglutide in diabetic kidney disease, the array of treatments available to help preserve kidney function has expanded greatly over a short period of time. Older patients – including those with frailty – can benefit greatly from the provision of these therapies [42]. Nephrologists can support primary care providers by helping evaluate those older persons who would benefit most from these therapies [42]. As part of the larger discussion undertaken with older adults centered on quality of life, long term goals of care, and overall health measures, approaching CKD in the older population offers the field of nephrology an opportunity to strengthen partnerships with primary care providers to improve kidney care delivery.

Abbreviations

CKD	Chronic Kidney Disease
ESKD	End-Stage Kidney Disease
RAAS	Renin-angiotensin-aldosterone system
GFR	Glomerular filtration rate
UACR	Urine albumin to creatinine ratio
ACE	Angiotensin converting enzyme
ARB	Angiotensin receptor blocker
SGLT2	Sodium-glucose transporter type 2
GLP1	Glucagon-like-peptide-1

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Competing interests

BMB has served on Data Safety Monitoring Boards with Omeros. GMC has served on the Board of Directors of Satellite Healthcare, a non-profit dialysis provider, as Chair or Co-Chair of Trial Steering Committees with Akebia, AstraZeneca, CSL Behring, Sanifit, and Vertex, and as an Advisor to Alexion, Applaud, Ardelyx, Calico, CloudCath, Durect, Eliaz Therapeutics, Miromatrix, Outset, Renibus, and Unicycive. He has served on Data Safety Monitoring Boards with Bayer, Mineralys, and ReCor.

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