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Special considerations in the management of chronic kidney disease in the elderly

Katharine Lana Cheung, MD[1], **Sandeep Soman, MD**[3], and **Manjula Kurella Tamura, MD, MPH**[1,2]

[1]Division of Nephrology, Stanford University, Palo Alto, CA

[2]Geriatric Research and Education Clinical Center, Palo Alto Veterans Affairs Health Care System, Palo Alto, CA

[3]Division of Nephrology, Henry Ford Hospital, Detroit, MI

Introduction

Chronic kidney disease (CKD) is a major health problem worldwide and in the United States CKD affects 27 million Americans and is the ninth leading cause of death[1]. It is increasingly prevalent in the elderly, estimated to affect 40% of persons older than 70 years[2]. The detection and management of CKD in this population presents several challenges due to the reduced accuracy of methods to assess kidney function and the high prevalence of coexisting conditions that may complicate CKD care. In this editorial we highlight several issues critical to the effective management of CKD in the elderly: assessment of kidney function, medication management, and hypertension control.

Assessment of kidney function in the elderly

The ideal method for assessment of kidney function in the elderly has yet to be determined but is of vital importance for Nephrology clinical care. Glomerular filtration rate (GFR) is currently accepted as the best overall index of kidney function, and as such it assumes central importance in the current NKF Kidney Disease Outcomes Quality Initiative (KDOQI) CKD staging system.

The gold standard measure of GFR, inulin clearance, is not practical in most clinical situations given its cost and time intensiveness. Measurement of creatinine clearance from 24-hour urine collections approximates GFR and may be useful in certain circumstances, but this method is also cumbersome and susceptible to collection errors. Thus, equations which estimate GFR from the serum creatinine concentration have been widely adopted into clinical care. The use of these equations has facilitated greater recognition of CKD, but it has also led to debate as to whether these equations over-diagnose CKD in the elderly. This concern is due to the fact that the two most commonly used equations, the Cockcroft-Gault (CG) equation and Modification of Diet in Renal Disease (MDRD) Study equation, systematically underestimate measured GFR[3]. A related concern is that prognosis for a given level of estimated GFR varies substantially by age.

Recently, a new equation to estimate GFR, the CKD Epidemiology Collaboration (CKD-EPI) equation has been introduced[4]. Preliminary reports indicate the CKD-EPI equation has

Corresponding author: Manjula Kurella Tamura, MD, MPH, Division of Nephrology, Stanford University, 780 Welch Rd, Suite 106, Palo Alto, CA 94304, Phone: 650-721-6617, Fax: 650-721-1443, mktamura@stanford.edu.

improved precision and accuracy compared to the MDRD or CG equations[5]. Systematic underestimation of GFR appears to be attenuated; when applied to the United States population, the mean GFR is shifted upward by approximately 10 ml/min/1.73m^2. Of relevance to the elderly, the equation was derived and validated from clinical populations which included approximately 1500 subjects over the age of 65. Thus, use of the CKD-EPI equation may alleviate some, though not all of the concerns associated with GFR estimation in the elderly.

Like the CG equation and MDRD Study equation, the CKD-EPI equation relies on serum creatinine and thus is subject to the limitations of creatinine-based equations – namely that creatinine production is influenced not only by kidney function but by muscle mass. Measurement of cystatin-C, a constitutively expressed protein produced at a constant rate and eliminated solely by glomerular filtration, has been proposed as an alternative or confirmatory marker of kidney function. It is less influenced by muscle mass as compared to serum creatinine, and thus may be especially well-suited for assessment of kidney function in elderly patients with prominent sarcopenia[6]. In several large cohort studies of older individuals, cystatin-C predicted risk for mortality and end-stage renal disease more accurately than creatinine-based GFR estimating equations [7-8]. An important limitation of cystatin-C is the lack of laboratory standardization, as has recently been undertaken for serum creatinine. Thus, cystatin-C measurement appears promising, but has not yet been fully integrated into clinical care.

Medication issues in elderly patients with CKD

In addition to its central role in CKD risk stratification, accurate assessment of kidney function is important is the dose adjustment of medications cleared by the kidney. Pharmacokinetic studies, following guidance from the Food and Drug Administration, have been conducted using the CG equation to estimate kidney function, while most clinical laboratories report estimated GFR according to the MDRD Study equation[9]. A recent study indicates that substitution of the MDRD Study equation for the CG equation would lead to similar drug dosage adjustments for several commonly used drugs[10]. Direct measurement of GFR should be considered for drugs with serious toxicity or a narrow therapeutic index, and in frail patients who are more likely to have inaccurate assessments of kidney function using estimating equations.

CKD and advanced age may also affect drug bioavailability. For example, some CKD medications, such as aluminum or calcium based phosphate binders may reduce the oral bioavailability of some antibiotics or iron-containing supplements when co-administered [11]. Volume of distribution and total body water are reduced in the elderly, while CKD may affect drug volume of distribution in unpredictable ways. Elderly patients with CKD may also have reduced protein synthesis and/or proteinuria, which may result in higher than expected plasma concentrations of protein bound drugs.

In addition to drug dosing, polypharmacy can also complicate CKD management and increase the risk for adverse events. The average elderly patient with CKD is prescribed 5 or more medications [12]. Elderly patients commonly use non-prescription medications too, and these may be underreported. Polypharmacy, as well as low health literacy and impaired cognition may in turn affect medication adherence[12]. Medication adherence may be improved and adverse drug events reduced by conducting comprehensive geriatric assessments including medication reconciliation at each visit and by incorporating pharmacists into CKD multidisciplinary teams[13].

Hypertension control in elderly patients with CKD

Treatment of hypertension in CKD patients is aimed at lowering mortality risk, slowing progression of CKD and preventing cardiovascular events. In elderly patients with CKD the risk for each of these events is not equivalent. For example, for patients over age 75, the risk of death is higher than the risk of progression to ESRD, even when CKD is advanced[14]. Thus, slowing progression of CKD may not be the main priority in an elderly patient with CKD. KDOQI guidelines for hypertension management in CKD currently recommend targeting a blood pressure less than 130/80 mm Hg; however the studies upon which these recommendations are based included few elderly patients. While there is good evidence that treatment of hypertension reduces morbidity, even in elderly persons[15-16], there is uncertainty about the optimal blood pressure target, particularly in elderly patients with CKD[17]. For example, some observational evidence suggests morbidity and mortality are higher in elderly patients with CKD who have systolic blood pressure below KDOQI targets [20].

The theoretical benefits of lowering blood pressure to the targets recommended in clinical practice guidelines must be balanced by the potential risks in elderly patients with hypertension. Orthostatic hypotension in the elderly with CKD is a common complication of hypertension treatment and the causes are frequently multifactorial. Age-related decline in baroreceptor reflex sensitivity, decreased alpha -1-adrenergic responsiveness to sympathetic stimuli, decreased water and salt conservation, increased vascular stiffness and reduced left ventricle compliance have all been suggested as predisposing factors in elderly patients[21]. Medications commonly implicated in orthostatic hypotension and frequently used in an elderly population are terazosin, furosemide, lisinopril and hydrochlorthiazide[22]. Certain co-morbid conditions, such as diabetic autonomic neuropathy may also contribute.

The management of orthostatic hypotension should be driven by the specific etiologies. All elderly patients, regardless of symptoms, require proper measurement of blood pressure in sitting and standing positions to determine if orthostatic hypotension is present. This is critical because the absence of symptoms does not preclude the potential risks associated with falls or syncope. Several experts recommend titrating blood pressure medications to standing rather than sitting blood pressure measurements in order to reduce fall risk. Potential culprit medications should be eliminated and alternate anti-hypertensive medications substituted. If symptoms persist, the potential benefits of lower blood pressure target must be weighed against the risks of adverse events, the burden of additional medications, and considered in the context of the patient's overall treatment goals.

Summary

The care of elderly persons with CKD may be complicated by several factors, including uncertainty about the accuracy and significance of low GFR estimates, age-associated pharmacokinetic changes and the high prevalence of polypharmacy, and co-morbid conditions. All of these factors make weighing the risks and benefits of CKD treatment strategies more challenging. When managing elderly patients, it is important to keep in mind that CKD clinical practice guidelines, such as those for blood pressure control, were largely developed in non-elderly populations with CKD. Thus, CKD treatment guidelines must be tailored to suit the individual patient and his or her treatment goals and preferences. Ultimately, achieving patient-centered care for the growing elderly population with CKD will require a more collaborative approach with pharmacists and geriatricians and individualized care plans that go beyond the guidelines.

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