The Elderly Patient with Low eGFR: Beyond the Numbers

MAROUN AZAR, MD

ABSTRACT

Chronic Kidney Disease (CKD) is widely prevalent in the elderly population. The recent "Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline on the Evaluation and Management of CKD" builds on the previous Kidney Disease Outcomes Quality Initiative (KDOQI) guideline and addresses many of its gaps. However, older adults with CKD have unique characteristics that may not be addressed by general guidelines. This review presents many of the challenges and considerations in the care of elderly patients with CKD, with the ultimate goal of promoting an individualized management plan based on shared decision-making.

KEYWORDS: chronic kidney disease, elderly, prognosis, conservative management, shared decision-making

INTRODUCTION

The introduction of the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines by the National Kidney Foundation (NKF) in 2002 established the classification of chronic kidney disease (CKD) based on glomerular filtration rate (GFR) or realistically, estimated GFR (eGFR) [1]. Applying this classification to the NHANES 1999-2004 cohort, it was estimated that 16.8% of the US general population has CKD. The prevalence was much higher, 39.4%, in those aged 60 and older, most of whom have early stages of CKD [2]. This raised concern that CKD may be over diagnosed, especially in the elderly without albuminuria, since some decrease in eGFR may simply represent normal kidney aging. The Kidney Disease: Improving Global Outcomes (KDIGO), now independent from NKF, published new CKD guidelines in early 2013. Among the numerous updates were the addition of albuminuria - a major prognosis modifier - into the classification by GFR, the division of CKD stage 3 into 3a and 3b, focus on CKD outcomes, guidance on specialist referral and promotion of multidisciplinary CKD chronic care models, including the ability to provide conservative (non-dialytic) management (CM) [3]. Age, however, was not incorporated into CKD classification and the issue of kidney senescence versus disease still stirs debate [4]. While the referral rate for CKD has increased significantly since 2002, there continues to be a surprising lack of guideline awareness among many non-specialists. Older patient age, among other factors, tends to decrease the odds of referral [5]. Certainly, not all elderly with CKD may benefit from specialist care, but many would. Older adults have unique characteristics. The following sections will review several key considerations relevant to the care of older patients with low eGFR.

DIAGNOSTIC CHALLENGES: KIDNEY SENESCENCE OR DISEASE?

Kidney Senescence: selected attributes

Most anatomical and histological changes attributed to kidney aging stem from cross-sectional studies such as autopsies and biopsies. The number of glomeruli is determined prenatally and varies widely from 330,000 to 1,100,000 among adults. Renal mass generally starts decreasing around the 4th decade of life, which may also be seen radiographically and corresponds mostly to cortical loss. Histological changes on light microscopy are generally termed "nephrosclerosis" and include glomerulosclerosis, arteriosclerosis, tubular atrophy and interstitial fibrosis [6]. In a large cohort of living donors at the Mayo Clinic, the prevalence of nephrosclerosis varied from 2.7% at ages 18–29 to 75% at ages 70–77 [7].

Functionally, there are very few longitudinal studies looking at decline in GFR. Perhaps the most notable is the Baltimore Longitudinal Study of Aging, where 254 "normal" adults of ages 22–97 were followed with serial (5–14x) creatinine clearance (CrCl) measurements from 1958–1981. Overall, there was an average decline in measured CrCl (mCrCl) of 0.75 mL/min/year but there were 3 patterns: a group with slow decline in serial mCrCl, a group with faster decline and a group with no change to a small improvement[8]. This led some to believe that renal functional decline with age is not universal. However, it is important to note that diabetics were not excluded if they had no proteinuria (diabetes may be associated with an initial increase in GFR due to hyperfiltration) and CrCl measurement itself is not without flaws. Nonetheless, it has been widely quoted since that "GFR" decreases at an average rate (0.75–1 mL/min/1.73m2/year) in healthy aging.

Living donors, being especially well screened, are typically a good representation of "healthy" older adults, although some may have treated hypertension. The Mayo Clinic cohort mentioned above offers some additional notable observations (cross-sectional): GFR overall declined by age;

none of the 1203 donors (max age 77) had a measured GFR (mGFR) < 60 mL/min/1.73m2 (using iothalamate); there was no correlation between mGFR and nephrosclerosis; the only characteristics associated with nephrosclerosis independent of age and sex in this healthy population were urine albumin, nocturnal blood pressure, and treated hypertension; finally, 5% would have had CKD by eGFR, but had normal mGFR and no nephrosclerosis [7].

Measuring Kidney Function in the Elderly

Based on the above, a hypothetical healthy 90-year-old woman with no comorbidities, starting off with a GFR of 100 mL/min/1.73m2 and losing GFR after age 30 at an annual rate of 0.75, would have a GFR of 55 mL/min/1.73m2 that could be attributed to aging and not "disease." However, measuring GFR using exogenous substances (inulin) is not practical or readily available in many places and is replaced in clinical practice by estimates (eGFR). Most labs automatically report eGFR using the 4-variable MDRD or the more recent CKD-EPI equation. The latter is slightly more accurate [9]. While these equations are very practical and useful for epidemiological studies, it is important to remember that no matter which one is used, the difference between eGFR and mGFR can be substantial, in some cases more than 30 mL/min/1.73m2. The incorporation of cystatin C may improve the accuracy of eGFR [10] but is costly and not widely used yet. Measured creatinine clearance (mCrCl) is another option but it is cumbersome for many elderly and errors in collection are common. It may not necessarily be more accurate than eGFR, since it typically overestimates mGFR by a variable degree, which gets worse as GFR decreases, due to an increase in creatinine secretion by the proximal tubules and extra renal degradation. Surprisingly however, one study found that mCrCl underestimates mGFR in the elderly [11]. Still, it may be useful in extremes of weight, amputees, vegetarians and those taking creatine supplements [12], as all of these factors are not taken into account in eGFR equations.

Senescence or disease: does it matter?

Hard outcomes in the elderly with low eGFR

Studies in nephrology have traditionally focused on hard outcomes such as mortality and End-Stage-Renal-Disease (ESRD). From an epidemiological stand point, an association between moderately low eGFR (stage 3a) and poor outcomes is (arguably) useful in distinguishing kidney aging from CKD. Many such studies have provided conflicting results in the elderly. However, a very large recent meta-analysis encompassing intercontinental high risk and CKD cohorts totaling over 2 million patients (age 18 to >75 years), showed increased mortality and ESRD rates in all stages of CKD regardless of age category. The relative mortality in the elderly was attenuated but the absolute mortality was higher. Age did not affect ESRD risk [13]. Population–level associations however, may not necessarily apply to an individual patient. For example, the above meta-analysis also showed increased mortality at very high eGFR values in patients >55y, likely reflecting the influence of patients with muscle wasting (due to malnutrition or other comorbidities) [13]. Does that mean that a healthy and active 65-year-old individual with eGFR 100 mL/min/1.73m2 is at risk? Probably not. The same concept goes for an older adult with eGFR 50 mL /min/1.73m2. The new KDIGO CKD classification system does not distinguish between age groups [3]. The author agrees with this decision, with the acknowledgment that no guideline is designed to be a substitute for individual judgment.

THERAPEUTIC CHALLENGES IN THE CARE OF ELDERLY PATIENTS WITH CKD AND THE ROLE OF THE NEPHROLOGIST

General referral guidelines

The KDIGO guidelines suggest a list of criteria for referral to a nephrologist. These include: Acute kidney injury (AKI), CKD stage 4-5, significant albuminuria or proteinuria, progressive CKD, RBC casts, unexplained hematuria, refractory hypertension, persistent serum potassium abnormalities, recurrent and extensive nephrolothiasis and hereditary kidney diseases[3]. Some of the benefits of early versus late referral include: reduced mortality and hospitalization, better uptake of peritoneal dialysis and earlier placement of dialysis access [14]. Patients with early stages of CKD often can be managed by their primary care providers (PCP).

Traditional facets of typical CKD care, some of which may be done by PCPs, may include treatment aimed at delaying progression, managing complications such as anemia, bone-mineral disorders, hyperkalemia, metabolic acidosis, blood pressure and glycemic control, correct dosing of medications, preparing for ESRD and other interventions aimed at cardiovascular risk reduction.

Beyond the guidelines

Regardless of whether reduced eGFR is attributed to aging or CKD, the older adult with low eGFR presents unique challenges. Many interventions are often of unproven benefit and sometimes harmful in the elderly. Outcomes of particular interest to the elderly, such as maintaining independence and quality of life (QOL), are often lacking in many clinical trials. Older adults with limited life expectancy may not live long enough to realize the benefits of certain therapies. Guidelines are inherently incapable of addressing individual situations and may conflict with recommendations aimed at another comorbidity. It is up to the provider to reconcile guidelines with patient preferences and to individualize therapy after judging risk/benefit ratio. For example, in an 85-year-old frail hypertensive woman with CKD and frequent falls, it may be unsafe to aim for a blood pressure of 130/80 mmHg. In a similar patient who has hyperphosphatemia, the increased pill burden of phosphate binders may

outweigh the potential long- term benefits.

In an interesting survey of provider decision-making, the strongest factor that influenced PCP decision to refer older adults with CKD was the expectation that the nephrologist will discuss goals of care. Initiation of dialysis per se was not a factor [15]. Decades after its introduction, dialysis therapy has boomed and has automatically been assumed to prolong life. However, the elderly population with ESRD often has poor outcomes and very high mortality rates [16]. CM may be a better alternative for some of them. The nephrologist's role includes assessing, educating and counseling elderly CKD patients and their caregivers to determine the best course of action in the event of ESRD. Estimation of CKD prognosis and understanding outcomes of renal replacement therapy (DT) versus CM (including outcomes that may be relevant to the patient, other than mortality) is crucial for proper "shared decision-making" to occur.

Who progresses to ESRD?

In a very large VA cohort (n = 209,622) with CKD stages 3-5 followed for a mean of 3.2 years, risk of death was higher than risk of treated ESRD in adults >65-84 years of age for eGFR >15 mL/min/1.73 m2. For adults >85 years age, mortality always exceeded risk of treated ESRD. There was not enough information to identify patients who had indications for DT but elected not to start it [17]. Complementing this information, a large community-based CKD cohort from Alberta, Canada (n=1,813,824) was studied retrospectively with a median follow up of 4.4 years. Among those 75 years of age and older, the rate of untreated ESRD was significantly higher (2–10 fold) than the rate of treated ESRD, while the opposite was observed in younger adults. Possible reasons for this include a competing risk of death in older adults, lower rate of uremic symptoms or less acceptance to RRT and transplantation. Still, the rate of combined treated and untreated ESRD was elevated in the elderly [18]. According to USRDS data, the elderly show the highest ESRD incidence and prevalence rates [16].

Using the rate of eGFR decline to predict ESRD is intuitive. However, what constitutes rapid progression is controversial. Data from the Alberta Kidney Disease Network show a graded increase in treated ESRD risk of approximately 2-fold for each 1 mL/min/1.73m2/year increase in eGFR decline slope. Albuminuria is also a major risk factor although changes in albuminuria over time require more studies [3].

However, CKD progression is often non-linear. Acute kidney injury (AKI) can significantly alter the course of CKD. A meta-analysis (n=5529 patients) showed that patients 65 and older with AKI were 28% (95% [CI] 1.01- 1.55, p<0.05) less likely to recover renal function than younger ones [19]. In a US cohort of 233,803 hospitalized elderly patients who survived to discharge, the adjusted hazard ratio for developing ESRD was 41.2 (95% [CI] 34.6 to 49.1) for patients with AKI and CKD relative to those without kidney disease, compared to 8.4 (95% [CI] 7.4 to 9.6) for patients with CKD and without AKI [20]. There is growing interest in predictive models for CKD progression to ESRD. For example, Tangri et al. developed and validated a predictive model of kidney failure from 2 large Canadian cohorts with CKD stage 3–5 [21]. It is available online and in mobile applications such as QxMD. Drawz et al. developed and validated a 1-year predictive model from 2 VA cohorts, which was comparable to Tangri's model in the validation cohort (C-index 0.823 vs 0.780 respectively) [22]. While the utility of these models needs to be evaluated prospectively, they may be useful in the shared decision-making process. Caution is warranted however, when using them (if at all) in populations with different characteristics than the original cohorts.

Survival with or without DT

While older adults can have favorable outcomes after kidney transplantation, the reality is that only very few get this opportunity – 3.4% of ESRD patients 70 or older, 0.5 % of patients 80 and older [23]. This topic is beyond the scope of this review.

In the absence of randomized controlled trials of CM versus DT, retrospective studies offer important insights. In a UK cohort of elderly ESRD patients (n = 129), DT provided better survival (measured from when eGFR <15) compared to CM (12 months of multidisciplinary treatment - MDT). However, patients with high comorbidity scores, especially ischemic heart disease, did not have better survival on DT compared to CM [24]. In a larger UK cohort (n = 844), DT only provided a marginal, non-statistically significant survival advantage of 4 months (measured from a putative eGFR in CM patients) when adjusted for age >75, comorbidity and diabetes [25]. From a different perspective, another UK observational study of 202 elderly patients showed an advantage of DT compared to CM (37.8 versus 13.9 months). However, DT patients had significantly more hospital days and CM patients were more likely to die at home. When accounting for hospital days and time spent on dialysis (whole day for many patients), the difference in "hospital/dialysis free" survival shrinks between the 2 groups to just a few months [26].

There is also interest in predictive mortality models for incident and prevalent dialysis patients. For example, Cohen et al. developed and validated a prognostic tool to estimate 6-month mortality in prevalent dialysis patients in the US [27]. It is available online and in some mobile applications.

Tamura et al. provide a useful framework for individualizing decisions in elderly ESRD patients by considering life expectancy, risks and benefits of competing treatments (including "number needed to treat" comparisons) and patient preferences. They apply it to choice of dialysis modality, choice of dialysis vascular access and referral for transplantation [28]. Using a predictive model to calculate life expectancy would come in handy when following such framework.

Other important outcomes and considerations

Frailty (and geriatric syndromes in general) is very common in elderly CKD patients. Prevalence dramatically increases with CKD stage and is associated with increased mortality [29]. In a US cohort (n=2275), 78.8% of ESRD patients > 80 years of age met criteria for frailty and had more than 2-fold increase in mortality [30]. Nursing home incident ESRD residents (n=3702) were studied linking USRDS data with Minimum Data Set–Activities of Daily Living (MDS–ADL) scores. Patients experienced a sharp decline in functional status in the first 3 months after dialysis initiation. At 1 year, 58% had died and only 13% had maintained their functional status [31]. Similarly, initiation of dialysis had a negative effect on independent living in a community of patients > 80 years old [32].

Functional status of ESRD patients managed by CM was preserved until the last month before death in a UK single center study [33]. Symptoms in the last month can be significant and may require an integrated multidisciplinary palliative care approach [34].

QOL was assessed in a single UK center in a cohort of patients with ESRD treated with RRT versus CM (n = 170, mean age >70, follow up 3 years). CM patients were older, more dependent, had higher comorbidities, poorer physical health and more anxiety at baseline. Mental health, depression symptoms and global satisfaction with life were similar in all modality groups at baseline. SF-36 and anxiety scores changed little during follow-up in both groups. Satisfaction with life scores decreased significantly after dialysis initiation and did not subsequently recover, but did not change over time in the CM group [35].

Shared Decision Making

Discussing all the elements above and aligning CKD management with the patient's goals of care is at the heart of patient-centered medicine. An interesting Australian survey in CKD 3-5 patients (n=105 completed) aimed to asses factors influencing patient choice of ESRD treatment. Patients were more likely to chose RRT over CM if it increases life expectancy, if it can be done during the day or evening versus day only and if subsidized transport was available. They were more likely to chose CM if RRT meant more hospital days and more restrictions on travel. Patients would trade off 7 months of life expectancy to reduce hospital visits and 15 months of life expectancy to increase ability to travel [36]. Unfortunately, elderly patients are often marginalized in the decision to undergo RRT and are left with many misconceptions.

The Renal Physicians Association offers updated guidelines on shared decision making in ESRD (http://www.renalmd.org/catalogue-item.aspx?id=682).

US Concerns and challenges

Most of the data on CM coming from other countries, there are concerns that its implementation in the US is challenging due to "uneven access to palliative care across health care systems, a shortage of palliative-care physicians, limited training of US nephrologists in these areas, and poor reimbursement for these and other cognitive services" [37]. Furthermore, patient choices and goals of care may not agree with the growing number of imposed reportable and penalizable "quality measures," many of which are of questionable utility, especially in the vulnerable elderly. This introduces conflict of interest when practices may be faced with financial penalties.

However, the US healthcare system is constantly evolving. The interest in patient-centered medical homes is extending into patient-centered neighborhoods, with the promise, if done correctly and with fair incentives, of addressing many of these concerns [38, 39].

The dramatic increase in dialysis rates in the US seems to be substantially slowing down recently, suggesting later dialysis starts and greater use of CM [40].

On an international level, KDIGO convened a "Controversies Conference on Supportive/Palliative Care in CKD" in December of 2013 in Mexico, which can be reviewed online (http://kdigo.org/home/conferences/supportivecare/).

CONCLUSION

The elderly population with CKD is growing fast and often has poor outcomes. Guidelines provide guidance as to the management of CKD but older adults present unique diagnostic and therapeutic challenges that go beyond simple numerical targets. Collaboration between primary providers and nephrologists, often within larger multidisciplinary teams may optimize the care of these individuals through better counseling and a process of shared decision-making. Many may be better served by CM. Obstacles are numerous but can gradually be overcome by the concerted efforts of all the involved parties.

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Author

Maroun Azar, MD, is Assistant Professor of Medicine, Alpert Medical School of Brown University, Division of Kidney Diseases and Hypertension, Rhode Island Hospital, VAMC of Providence & Kent Hospital.

Disclosures

None

Correspondence

Maroun Azar, MD
593 Eddy St, APC 9,
Providence, RI 02903
401-444-5445
Fax 401-444-6849
maroun_azar@brown.edu