Chronic kidney disease in older people: a cause for concern?

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The introduction of estimating equations which take account of markers of muscle mass increases the sensitivity of detecting reduced kidney function compared to use of serum creatinine alone [1]. A consequence has been the recognition in many studies, both health surveys and using clinical biochemistry laboratory data, of the very high prevalence of reduced kidney function in older people [2–4]. Moreover, routine reporting of estimated glomerular filtration rate (eGFR) by clinical biochemistry laboratories and the high rates of blood testing for serum creatinine for the investigation of older people, means that significant numbers of older people with reduced kidney function are being detected in routine clinical practice [4].

The five stage classification system of chronic kidney disease (CKD) with the use of the term ‘disease’ has fuelled considerable debate as most people with >50% loss of function, labelled CKD Stages 3–5, are older people [5]. For example, in the 2009 Health Survey for England of those diagnosed with CKD Stages 3–5, 50% were aged >75 years and another 25% aged 65–74 years [6]. Introduction of the more accurate Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula instead of Modification of Diet in Renal Disease (MDRD) would increase the proportion of cases diagnosed with CKD who are elderly [7]. While the clinical significance of such reduced kidney function in older people has been questioned, policy initiatives, which focus on the detection and management of CKD 3–5, such as the UK’s Quality Outcomes Framework for Primary Care, have been introduced in some countries.

Several questions are raised. Is reduced kidney function in older people just a benign phenomenon associated with the physiological ageing process or do co-existing conditions? [8, 9] Should age gender-specific reference values or cut points be used for staging? Even if CKD is associated with adverse health in older people does it justify labelling it as a disease with the consequent personal and social implications? What are the relative and, as important, the absolute risks of important health outcomes associated with CKD in older people and how do these compare to younger ages, i.e. is there an interaction of age with measures of CKD for key outcomes? What are the implications for clinical practice for assessing prognosis and for modification of such risk in older people, and the most cost effective and appropriate interface between nephrology services and primary and other non-specialist care given the scale of the numbers of older people with CKD? What are the implications for practitioners and policy makers of the demographic transition in high-income countries, with an increasing prevalence of older people with a high chronic disease burden including CKD associated with greater health care use and multiple co-morbidities. The epidemiological and demographic transition in middle- and low-income countries makes this an emerging global issue.

The article by Stengel et al. [10] in this issue addresses several pertinent questions in a population-based prospective cohort study in France of the >65s: the prevalence and gender differences in clinically relevant and potentially modifiable markers associated with CKD such as albuminuria, resistant hypertension and anaemia; the rate of CKD progression; comparison of MDRD versus CKD–EPI equations in relation to prevalence and mortality risk and the prognostic impact of stages of CKD on all-cause mortality (ACM) and cardiovascular mortality. Key findings were: derivation of estimates of the prevalence of adverse markers which increased as kidney function fell and which were greater in men; kidney function declined with age even in those who were apparently healthy (found by others [11]); a significant proportion of older people had a rapid decline and this was often not associated with markers of kidney damage; that in this study, MDRD...
and CKD–EPI provided similar estimates of risk, though use of CKD–EPI reduced prevalence and gender differences and showed a steeper relationship with age; and that CKD 3b (eGFR < 45 mL/min/1.73 m²) was associated with poorer ACM survival, though cardiovascular disease (CVD) mortality risk was increased in all with Stage 3 CKD. An important implication for clinical practice discussed by the authors is that among the large prevalent pool of older people with CKD 3–5, more focus could be given to referral and intervention in those with eGFR <45, especially the minority with potentially modifiable markers which trigger evidence based interventions, which includes not only proteinuria but also anaemia and resistant hypertension.

There are several important health outcomes to consider for assessing the impact of reduced kidney function (eGFR) and kidney damage (albuminuria) in older people. Many studies have studied ACM or CVD mortality and there is good evidence that these outcomes are much more common than kidney-related ones in older people [12, 13]. Other outcomes of relevance for older people include kidney disease progression, incident end-stage renal disease (ESRD), acute kidney injury, non-CVD events (e.g. cancer, hip fracture and infection), hospitalization rates, quality of life, depression, functional status and cognitive decline.

In relative terms, the risk of ACM associated with declining eGFR has been shown to fall with increasing age [14, 15]. In a UK study of Raymond et al. [14], based on laboratory testing for serum creatinine, relative risk associated with Stage 3a fell progressively from 13.6 in 20–44s to 1.2 in 75–84s and 0.9 in ≥85s. The study of O’Hare et al. [15] of US Veterans, predominantly males and also using routinely laboratory data, had similar findings with no significant effects of eGFR 50–59 in ages >65 on adjusted analysis. In both studies, the absolute risk difference for older age groups was similar in mild/moderate CKD and greater in more advanced CKD.

The CKD Prognosis Collaboration has added extensive new data on the prognostic significance of low eGFR and albuminuria based on pooling of data from population and high-risk cohorts and has studied age/eGFR and age/albumin to creatinine ratios (ACR) interactions. Both MDRD eGFR and ACR were independent factors associated with ACM and CVD mortality in general population cohorts (21 studies, 1.2 million participants) and in high-risk cohorts (10 cohorts, 0.27 million participants) [16, 17]. Meta-regression in general population cohorts found no age interaction at eGFR of 45 mL/min, though hazard ratios were higher in younger ages for both ACR and eGFR of 60 mL/min. Some high-risk population cohorts had significant age eGFR and age ACR interactions; overall, the age eGFR slope was less steep in older people for ACM, though more similar to younger ages for CVD. Dividing age into above and below 65, the hazard ratios were similar for CVD but lower for ACM [18]. The study by Stengel et al. [10] also identified an important sub-group with rapid decline in eGFR, which is associated with increased CVD risk [19], highlighting the need to assess progression rate.

Misclassification using MDRD-derived eGFR may affect risk estimates as MDRD was not validated in older people; Stengel et al. [10] found similar risk estimates with CKD–EPI. Any attenuation of relative risk in older ages is probably largely due to the high underlying risk of mortality in the referent group. The impact of CKD on mortality and non-fatal CVD in older people will be determined by the absolute risks in the population, CKD prevalence and the relative effects of eGFR or ACR. More work on impact is needed though recognizing that absolute risks will be much more variable between populations than relative risks.

In the CKD Prognosis Collaboration, both eGFR and ACR were independent risk factors for all kidney outcomes (ESRD, progression and acute kidney injury (AKI)) in general and high-risk population cohorts [20]. The slopes were generally less steep in older people but of similar shape, and hazard ratios were similar at ages above and below 65 [18]. eGFR and ACR were usually stronger risk factors than age, in contrast to mortality outcomes where age was dominant. Using need for dialysis to define ESRD may underestimate progression to ESRD in older people. There is emerging evidence that the increased risk of AKI is found at higher levels of GFR than risks for ACM or CVD [21, 22]. The incidence of AKI rises with age, for dialysis and non-dialysis requiring, and it has risks of short and long term mortality, increased hospitalization and greater risk of ESRD in older people [23–26]. Given the high prevalence of CKD in older people and the increased risk of exposure to renal insults (e.g. from major surgery, medication, acute illness), AKI on CKD in older people is a growing public health problem.

Fried et al. [27] showed that reduced kidney function (using Cystatin C) was associated independently with increased risk on non-cardiovascular mortality, but with no single-specific cause, therefore, including cancer, infection and respiratory disease. This risk was apparent at eGFR <60 mL/min. In a population-based study of >75s Nitsch et al. [28] showed significant independent effects of eGFR <30 mL/min and dipstick on risk of hospitalization and repeat hospitalization >2 years follow-up. Hip fracture mortality was also increased at eGFR <45 mL/min, others have found increased risk of incident hip fracture with CKD (at eGFR <60 mL/min and in a study using Cystatin C) [29–31]. In the study by Roderick et al., the prevalence of predicted adverse consequences of reduced function were increased in the smaller sub-group with eGFR <45 mL/min (e.g. anaemia, phosphate retention, low albumin) as were poor function, dependence, lack of activity and quality of life; similar findings for anaemia were found in an Australian study of older people [32, 33]. Reduced kidney function is associated with malnutrition and frailty in older people [34–36].

An eGFR <45 mL/min in older people is at the very least a marker for vulnerability and combined with ACR a strong-independent predictor of mortality and serious morbidity. What is less clear is the significance of eGFR at 45–59 mL/min especially those without a raised ACR though the emerging evidence certainly identifies the risk of AKI. Cystatin C may provide more accurate risk prediction in older people whether alone or combined with serum creatinine-based eGFR and ACR, although at increased health care cost and organizational change as it is not a routine test. Cystatin C has prognostic significance for mortality in the elderly, and in the Regards study (subjects over age 45 years), a triple test improved the prediction of ACM and ESRD when Cystatin C was added...
to serum creatinine eGFR and ACR [37, 38] Further work is needed to assess the change in prognostic accuracy in older people of using Cystatin C especially those with chronic eGFR of 45–60 mL/min.

The gender difference in the consequences of CKD found by Stengel et al. [10] may partly reflect systematic under-ascertainment of true GFR by the MDRD Study equation in women, although it was not clear to what extent this differed with using CKD–EPI. It may also reflect biological differences in the response to a low eGFR. A population-based study in Norway of diagnosed Stage 3 CKD found that females had improved survival and lower rates of CKD progression before menopause and Stengel’s study showed this to be true in older ages [39, 40].

In conclusion, the paper by Stengel et al. supports the re-classification of Stage 3 into 3a and 3b as an eGFR <45 mL/min in older people is associated with increased risk of a range of fatal and non-fatal adverse health outcomes, risk being much less apparent in the 45–59 mL/min band [10, 18]. The challenge is how to use prognostic information based on eGFR and ACR to improve outcomes for older people and to best focus specialist care where it will have maximal benefit. Stengel et al. have highlighted some indicator conditions. More research is needed into the impact of interventions in older people in different risk strata, on health benefits and risks (e.g. due to over medication) and health care costs, and specifically for interventions-targeting eGFR and ACR [41]. Specific goals in older people might include not only reduction of risk of CVD and CKD progression but also avoidance of AKI, falls and fractures prevention, vaccination (e.g. influenza), addressing malnutrition and depression, targeting avoidance of hospital admission and treatment of anaemia. Management of CKD in older people is complex and needs to be more individualized than primarily disease (CKD) orientated, taking into account factors such as functional status, cognition, co-morbidity and social factors [42]. Evidence is particularly lacking for the oldest age groups with CKD in whom managing multiple co-morbidities and weighing risk and benefit will be most challenging. Finally, greater recognition is needed of the prevalence and impact of CKD in other chronic prevalent conditions in older people such as chronic obstructive pulmonary disease and heart failure.

Conflict of interest statement. None declared.


References

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