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Glomerular Filtration Rate and Aging: Another Longitudinal Study – A Long Time Coming!

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The conjecture that measured glomerular filtration rate (mGFR) declines with aging, perhaps inevitably, is supported by many studies in the early literature on the subject [1–3]. More recent publications have amply confirmed that declining mGFR occurs in 'healthy' and even 'very-healthy' subjects, such as living related donors for kidney transplantation [4, 5]. In addition, numerous epidemiological studies have described such declining GFR with aging in samples of apparently healthy populations studied with estimated GFR (eGFR) rather than mGFR [6, 7]. The studies with mGFR were limited to a relatively small sample size, especially in the elderly, whereas the epidemiological studies may have been confounded by inaccuracies in the eGFR equations in elderly subjects. Moreover, all these studies shared the same important limitation: they are cross-sectional in character and thus impaired by survival biases. Very few longitudinal studies are available in the literature [8]. The 'Baltimore Longitudinal Study of Aging', published in 1985, was seminal and frequently quoted [9]. Between 1958 and 1981, this study followed 254 apparently 'healthy' males, of varying age, with serial endogenous true creatinine clearances (Ccr), as an approximation of GFR. They found that the mean decline in Ccr was 0.75 ml/min/year, and that nearly one-third of these subjects had stable or even increasing Ccr with aging. However, this study had several limitations. The health status of the subjects was poorly described and an unknown number had type 2 diabetes, a disorder known to have a marked influence on GFR, even in the absence of proteinuria [10]. Moreover, GFR itself was not measured and 24 h endogenous Ccr is no longer recommended to estimate GFR because of lack of precision and high intra-individual, between test variation [11]. This last point is particularly relevant for longitudinal studies [12], as statistically significant slopes for a change of GFR or Ccr require many points of observation. Too few points were available in many patients in the Baltimore Longitudinal Study of Aging.

The study by Malmgren et al. [13] in the current issue of *Nephron* can be considered as partially remedying some of the deficiencies of earlier studies. Indeed, the authors followed eGFR, but not mGFR, using several established serum creatinine-based estimating equations in a large cohort of elderly Swedish women longitudinally for 10 years. They showed interesting results concerning the prevalence of chronic kidney disease (CKD) in the elderly, demonstrated the average decline of eGFR over time in the elderly and, lastly, examined the association be-

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tween decreased eGFR and mortality. These studies have particular meaning for the definition of what constitutes CKD in an elderly and aging population.

The Prevalence of CKD or 'Decreased GFR' in Aging Subjects

The threshold for accepting 'decreased GFR' for defining the presence of 'CKD' in the elderly is difficult to determine and is also the subject of heated debate [14, 15]. We, and others, have challenged the definition of CKD chosen in the 2013 KDIGO (for 'Kidney Disease Improving Global Outcome') guidelines, which consider CKD to be present in any subject, regardless of chronologic age, when the GFR falls persistently (>3 months) below a value of 60 ml/min/1.73 m^2 [16], even in the absence of other signs of kidney injury, such as proteinuria. We suggest that this non-age calibrated threshold leads to a substantial overestimation of CKD prevalence, especially in the elderly [17] and have proposed that CKD Category 3A (an isolated GFR between 45 and 60 ml/min/1.73 m^2) not be regarded as bona fide CKD in the elderly; thus, CKD Category 3B (an isolated GFR of <45 ml/min/1.73 m^2) becomes the 'new' threshold for CKD definition [14]. Very importantly, we emphasize the fact that this new proposal is only applicable in subjects without any albuminuria or other signs of kidney damage. Also, the chronicity must be confirmed by a persistent result after 3 months. The choice of GFR threshold for defining CKD has an appreciable impact on the epidemiology of CKD in the elderly, such as in the study reported by Malmgren et al. [13] in a recent issue of *Nephron*. This study shows that CKD Category 3A includes a very large proportion of the population and that this proportion increases greatly with aging. The absence of measured albuminuria is a limitation of the study by Malmgren et al. [13], and one cannot be certain of the true prevalence of CKD in this population. However, the majority of elderly subjects reach CKD diagnosis according to the decreased eGFR only, without any reference to albuminuria [16].

Another limitation of the study by Malmgren et al. [13] is the absence of mGFR values, as appropriately acknowledged by the authors. In the absence of mGFR values, the authors have elected to consider different creatinine-based equations to estimate GFR and thereby to evaluate the prevalence of CKD. Although the KDIGO recommended the CKD-EPI (for 'Chronic Kidney Disease Epidemiology Collaboration') equation to estimate GFR [16], the ideal choice of an eGFR equation is not so obvious in elderly people [18–20]. As shown by Malmgren et al. [13], the prevalence of CKD in the elderly population is highly dependent on the equation used to evaluate eGFR. The data from the study by Malmgren et al. [13] show that in elderly subjects, the prevalence of decreased GFR is higher with the Berlin Initiative Study [18] or the Lund–Malmö equations [19] as compared to the Modification of Diet in Renal Disease or the CKD-EPI equations [13, 18]. A definitive answer concerning the superiority of one eGFR equation over another is simply not possible from this study because mGFR was not available. We can just comment on the following facts: on one side, the Berlin Initiative Study equation has been specifically developed in an elderly population [18]; on the other side, the Lund-Malmö equation has been developed from a Swedish database [19].

The Slope of GFR with Aging

Within 10 years, the women in the study by Malmgren et al. [13] lost 22% of their initial eGFR. The mean loss was 16.6 ml/min/1.73 m^2 per decade, which is more than twice the rate of decline in Ccr observed in the male-dominated Baltimore study, as cited previously. Also, results differ between the present study and the Baltimore study regarding the proportion of subjects with stable or improving eGFR (a very low proportion of such subjects was observed in the Swedish study). However, direct comparison is difficult because age, health status, method of GFR assessment and length of follow-up were not similar between the 2 studies. Also, an important difference between the 2 studies could be explained by the way the analyses have been performed. Indeed, slope (of eGFR or Ccr over time) has been measured only in 314 women who survived for the 10-year period in the Swedish study, though the slope has been calculated in all patients in the Baltimore cohort with different follow-up periods [9, 13]. This analysis 'only in the survivors' is very important to keep in mind when interpreting the results of the study. Death is an important competing risk in this elderly population [21]. Two characteristics of the eGFR slopes, as described by Malmgren et al. [13], must be interpreted in the light of this competing risk: (i) the non-linearity of eGFR slope with time; in other words, the accelerated loss of eGFR between 75 and 85 years compared to the 70–75 years period and (ii) the difference in eGFR slopes observed according to baseline eGFR, the decrease being more exaggerated in patients with high initial eGFR values. Indeed, it could be suggested that patients with low baseline GFR and rapid decrease in GFR will die before reaching the 10 years period of observation. Therefore,

even if the slope description is of interest, it remains only applicable in this age range.

The Definition of CKD and Mortality Risk

The association between decreased eGFR (i.e. <60 ml/min/1.73 m^2) and mortality (global or cardiovascular) has been used as an important justification for the choice of the unique GFR threshold for CKD definition in the KDIGO guidelines [16]. However, such a unique 'prognosis-based' threshold for CKD definition is questionable for several reasons [15]: (i) this leads to a large gap between eGFR sensed to be the breakpoint to predict mortality (or other events), that is, 60 ml/min/1.73 m^2 [22] and eGFR actually observed in healthy populations [6, 7]. For example, in the healthy population described by van den Brand et al. [6], low normal eGFR value (defined as the percentile 5) is 94 and 85 ml/min/1.73 m^2 at 25–29 years, 67 and 70 ml/min/1.73 m^2 at 50–54 years and 44 and 51 ml/min/1.73 m^2 at 70–74 years for men and women, respectively. This gap between prognosis and 'real-life' results can only be decreased by using an age-calibrated definition of CKD [14, 23]. (ii) The prognosis-based threshold could be different according to the 'event' considered and/or the methodology used. For example, the first article suggesting that increased all-cause mortality risk was independently associated with decreased eGFR was published in 2004 by Go et al. [24]. The authors showed that patients with eGFR of 45–59 ml/min/1.73 m^2 have a higher risk of all-cause mortality compared to an eGFR of ≥60 ml/min/1.73 m^2. However, this increased risk disappeared completely when a subgroup of subjects with repeated measurement of eGFR was considered whereas the increased risk for cardiovascular death remained significant at 45–59 ml/min/1.73 m^2 in the same subset of subjects with repeated eGFR measures. (iii) Surprisingly, the 'prognosis' approach could lead to different CKD definitions if other GFR biomarkers, like cystatin C were considered. Indeed, the threshold for CKD diagnosis should move from 60 to 80 ml/min/1.73 m^2, as cystatin C-based equation results below this threshold were associated with worse prognosis (and this association was stronger than with creatinine-based equation) [25]. (iv) Age, by nature the most important variable for mortality prediction, is also an important variable in all estimating equations and could thus subsume all these associations.

Having underlined the limitations of such a 'prognosis-based' CKD definition, we cannot ignore the fact, once again, that this is the fundamental argument of the KDIGO guidelines. Moreover, this point should be discussed because the association of eGFR with mortality risk is certainly another interesting part of the study published by Malmgren et al. [13]. The authors found that the risk of mortality is significantly higher in the elderly population categorized as CKD 3B (or higher) than for Category CKD 3A. At first sight, the lack of significant association between Category 3A and mortality in elderly in the study by Malmgren et al. [13] could be considered contradictory with prior publications supporting the KDIGO guidelines for CKD definition. Indeed, in the first CKD-EPI consortium study [22], the reference value of eGFR used for the calculation of hazards ratio (HR) was 95 ml/min/1.73 m^2. Later in 2012, the same consortium, with Hallan as first author, focused on the variable of age [26]. In this analysis the risk of mortality was also found to be increased when eGFR was <60 ml/min/1.73 m^2 in all categories of age, when the reference value of eGFR for HR calculations was 80 ml/min/1.73 m^2, and not 95 ml/min/1.73 m^2. The authors thus implicitly accept as fact that the 'normal' GFR changes with aging. Moreover, Hallan's paper is subject to different interpretations based on how one selects the value of the eGFR for reference group for HR calculations. The Hallan analysis is compatible with an age-dependent effect on the threshold of eGFR for identifying an increasing risk (HR) for all-cause mortality, and it can be deduced that in patients >65 years, there is no significant higher risk of mortality associated with CKD Category 3A, the risk being significant only in CKD Category 3B. Other cross-sectional data from a large Canadian study also confirmed that life expectancy was similar in the elderly if CKD Category 3A or CKD Category 1–2 were considered [27]. The results found by the longitudinal study of Malmgren et al. [13] parallel these findings from cross-sectional analyses and support an argument for an age-calibrated eGFR for the definition of CKD even within the limitations of a 'prognosis-based' CKD definition.

In conclusion, the study by Malmgren et al. [13] is a welcome addition to the growing literature describing the evolution of renal function with aging. Taken as a whole, it supports the notion that a single, non-age stratified threshold value for eGFR to define CKD is not appropriate. The extent to which such absolute thresholds overestimate the prevalence of CKD in the elderly remains a valid topic for debate.

Disclosure Statement

The authors have no conflict of interest to declare.

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