AGEING AND THE GLOMERULAR FILTRATION RATE: TRUTHS AND CONSEQUENCES

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ABSTRACT

The process of glomerular filtration of plasma fluid has been known for over 160 years and the measurement of the rate of its formation (glomerular filtration rate, GFR) has been possible for over 80 years. Studies conducted in the 1930's to the 1950's clearly established that GFR declines, perhaps inexorably, with normal ageing, usually beginning after 30–40 years of age. The rate of decline may accelerate after age 50–60 years. This decline appears to be a part of the normal physiologic process of cellular and organ senescence and is associated with structural changes in the kidneys. In the last decade a new paradigm has been introduced in which the true or measured GFR is estimated (eGFR) by formulas based on serum creatinine levels and in which these estimates are applied to the diagnoses of chronic kidney disease (CKD) in the general population. These criteria for diagnosis of CKD include an absolute threshold for eGFR, unadjusted for the effects of age on the normal values for eGFR. A consequence of these criteria has been to overstate the frequency of CKD in the general population and to generate many "false positive" diagnoses of CKD. This paper discusses the known effects of ageing on GFR and the consequences of using a classification system for defining CKD that does not take into account the normal decline of GFR with ageing.

TRUTHS

The process of glomerular filtration has been recognized for over 160 years, since Ludwig in 1844 first proposed the physico-mechanical formation of a protein-free ultrafiltrate by the renal glomeruli [1]. Measurement of the rate of formation of the glomerular filtrate (GFR) did not achieve reality until 1926 [2, 3] and real precision was obtained as a result of the pioneering studies of A.N Richards [4] and Homer Smith [5] in 1934–1935, investigators who independently described the

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use of Inulin (a polysaccharide neither secreted nor reabsorbed by the renal tubules and which is freely filtered at the glomerulus) as a substance to measure GFR using the clearance method. The constant infusion of Inulin along with timed urine collection and plasma sampling with calculation of the Inulin Clearance (Cin) is now the "gold standard" for measurement of GFR. Since then numerous methods have been devised for assessment of GFR which approximate the Cin. One of these is the clearance of endogenous creatinine (Ccr), a substance produced in muscle by the non-enzymatic dehydration of creatine. The Ccr overestimates the Cin by about 22% due to the fact that creatinine is normally secreted by the renal tubule.

Many reports of the measurements of Cin or Ccr in aging subjects have appeared since the pioneering studies of Nathan Shock and his colleagues beginning in 1945 [6, 7]. Most of these studies have been cross-sectional and have rather uniformly shown that the GFR declines steadily with aging, beginning at age 30–40 years, with an apparent acceleration in the rate of decline after age 65–70 years [6–9]. In the original studies of Davies and Shock the average decline in GFR was 0.96 ml/min/year or about 10 ml/min/decade [7]. The filtration fraction (GFR divided by Renal Plasma Flow or RPF) tended to remain constant until about age 65 years and older [7]. Later studies carried out by Rowe et al [10] and Lindeman, Tobin and Shock [11] utilized Ccr as an approximate measure of GFR. In a series of reports from this group, in conjunction with the Baltimore Longitudinal Study of Aging and using both cross-sectional and longitudinal study design, the changes in Ccr consequent to ageing were examined in community-living, apparently "normal" men, 20–89 years of age. Among 548 normal subjects studied by Rowe et al [10] in 1976, the Ccr fell from 140 ml/min/1.73m2 at age 30 years to about 97 ml/min/1.73m2 at age 80 years. In longitudinal studies involving three or more Ccr measurements carried out over 12–18 months in 293 "normal" subjects, a similar pattern of decline of Ccr with age was again observed, with an acceleration in the rate of decline with advancing age. Importantly, the decline in Ccr was independent of blood pressure values and other co-morbid conditions affecting the elderly. In a later study (including many of the subjects studied by Rowe et al), conducted by Lindeman, Tobin and Shock [11] and reported in 1985, the Ccr was examined in 254 apparently "normal" men (some of whom had diabetes mellitus unaccompanied by proteinuria). In this study the "slope" of Ccr vs. time (or age) (in ml/min/year) became negative after age 39, and the rate of decline in Ccr slowly accelerated to reach a peak value of minus 3.25 ml/min/year after age 80 years (See Table I). The overall average

TABLE I
Endogenous Creatinine Clearance (Ccr) by Decade of Life in "Normal" Subjects (n = 254) (Adapted from Reference (11))*

Age Group (Years)	Mean ± SEM Ccr (ml/min)	Slope of Ccr (ml/min/year)
30–39.9	156 ± 5	+0.67 ± 0,4
40–49.9	145 ± 3	−0.32 ± 0.2
50–59,9	136 ± 2	−0.57 ± 0.2
60–69.9	119 ± 3	−1.24 ± 0.3
70–79.9	107 ± 3	−1.49 ± 0.3
80–89.9	94 ± 6	−3.25 ± 0.7
All ages	130 ± 2	−0.75 ± 0.1

* (note: Ccr overestimates true GFR (Cin) by approximately 22%).

decline in Ccr was −0.75ml/min/year. In longitudinal studies of Ccr carried out in the same subjects (5 or more Ccr over 12 months up to 24 years), the "slopes" of Ccr (ml/min/year) were greater than zero in 92 of the 254 subjects and less than zero in 162 of the 254 subjects. Among those with "statistically significant" slopes, 2 were positive (+1 to +3 ml/min/year) and 29 were negative (−1 to −7ml/min/year). The distribution of the GFR slopes was Gaussian rather than bimodal, suggesting that the process was of an "involutional" nature instead of the result of a superimposed disease acquired by some but not all individuals in the study. Overall, the authors stated that 36% of the subjects had "no changes" in Ccr when studied longitudinally. This latter observation needs to be interpreted with some caution since the period of observation (often less than 5 years) may have been too short in some subjects or the number of Ccr measurements too few to reliably detect a true change in Ccr over time. Wide dispersion of the results (standard error of the mean) may have precluded an accurate assessment of the true slopes of GFR change. In addition, an unstated number of subjects had diabetes mellitus, which is well known to associate with an increase in GFR during periods of poor control of glycemia (also known as "hyperfiltration"). Nevertheless, some investigators have interpreted these findings to indicate that a loss of GFR with ageing is not inevitable ([12, 13]). Contrariwise, we believe that the bulk of the available evidence supports the view that a decline in GFR is part of the normal biological process of senescence, and that it is a universal phenomenon developing as an individual ages beyond about 30 years of age. The decline in GFR associated with ageing is independent of the presence of hypertension or a change in cardiovascular performance ([14]) and is observed in indigenous societies in which hypertension does not occur ([15]). Of course, superimposition of the co-

morbid disorders developing in the elderly can and does have an influence on the rate of decline of GFR over and above the fundamental age-dependent decline in GFR. Women also show a decline in GFR with ageing, but have been less well studied than men. Since women start with a somewhat lower GFR (even after correction for size and muscle mass), the final value of GFR in advanced age is usually lower in women than in men.

The decline of GFR with ageing is universally accompanied by changes in renal structure [16, 17]. The percentage of glomeruli affected by global glomerulosclerosis increases steadily with advancing age, even in the absence of any co-morbidity (such as hypertension), and the overall number of functioning nephrons also steadily declines with ageing [18]. Individual functioning glomeruli also reveal both structural and functional changes with ageing [18]. The volume of renal cortex slowly diminishes in concert with the loss of nephron mass.

The biological mechanisms underlying the decline in GFR with aging remain a subject of intense investigation [17]. Currently, it is believed that the decline in GFR is a manifestation of a progressive change in the vascular tree, perhaps related to the effect of oxidative stress and telomere shortening, or perhaps linked to an action of angiotensin II [17–19]. The rise in filtration fraction (GFR/RPF) with ageing is consistent with this viewpoint. However, it may be difficult to sort out the effects of ageing per se and the effects of co-morbid conditions commonly accompanying the ageing process [17]. Progressive loss of nephron mass, global glomerulosclerosis, arteriolo-nephrosclerosis, and an increase in interstitial volume are regular, indeed expected, findings in "normal" aging [16, 17].

Thus, our conclusion is that GFR slowly decreases with ageing as a normal biological phenomenon linked to cellular and organ senescence, and that a low GFR in an elderly person, compared to the value found in a youthful person, is not necessarily a manifestation of a specific disease. This is not to say that specific diseases cannot be superimposed on the normal ageing process and thereby influence the rate of decline in GFR seen in individual patients.

CONSEQUENCES

The observation that GFR declines normally with age was of general interest but did not have major clinical consequences in the *diagnosis* of disease until the appearance of two connected events during the last decade. The first was the description in 1999 of a new equation [19] to estimate the GFR from a serum creatinine concentration, and the

second in 2002 was the development of a new classification system [20] for the diagnosis and staging of chronic kidney disease (CKD).

Formulas for estimation of Ccr from serum creatinine measurements had been in use for many years [20, 21], mostly for assisting in drug dosing of agents that were nephrotoxic or those which were eliminated largely by GFR. However, the formula described in 1999 by Levey and co-workers [19] was one of the first systematic attempts to derive an equation for estimation of GFR (eGFR) from the simple measurement of a serum creatinine value (See Table II). This equation was developed from an analysis of subjects enrolled in the Modification of Diet in Renal Disease (MDRD study), all of whom had established (non-diabetic) CKD and who had measurements using iothalamate clearance (Cio) as a surrogate for true GFR [19]. The values of eGFR (in ml/min/1.73m2) are calculated from the serum creatinine concentration (in mg/dL) using the modifier variables of age in years, gender and ancestry (black vs non-black) as surrogates for endogenous creatinine production and excretion (See Table II). The MDRD eGFR formula is not very accurate for assessing GFR above 60 ml/min/1.73m2 and requires additional modifications for different ancestries (e.g., Chinese) [22, 23]. It also may not be applicable to subjects with regular diets different from those used to derive the formula (e.g. strict vegetarians). In subjects with established CKD and a true measured GFR of <60ml/min/1.73 m2 (Cin or Cio or another equivalent method) the accuracy may be better than in those with normal renal function, but the estimates still show wide standard deviation about the mean for the estimate [22], averaging about 14 ml/min/1.73m2. The bias for the MDRD eGFR relative to the measured GFR is relatively small, understating true GFR by about 1 ml/min/1.73m2 overall (a higher negative bias is present at higher eGFR) [22]. The formula is best used when the serum creatinine is calibrated to an authenticated "standard" since the uncalibrated values will vary from laboratory to laboratory due to the use of different methods for creatinine assay and standards used [24]. A modified re-expressed MDRD equation needs to be used when a calibrated standard is used for serum creatinine determination [24]. At the present time, the MDRD equation is used by most laboratories (hospital and commercial) for calculation of eGFR whenever a serum

TABLE II

The Modification of Diet in Renal Disease (MDRD) Formula for Estimating Glomerular Filtration Rate (eGFR). (From Reference (19))

Estimated GFR (eGFR) in ml/min/1.73m2 = 186 × (Serum creatinine in mg/dl)$^{-1.154}$ × (Age in years)$^{-0.203}$ × (0.742 if female and 1.21 if African-American)

creatinine is measured. In several states in the USA and in the United Kingdom and in Australia it is mandatory that eGFR be reported with every serum creatinine measurement. The reports give the actual calculated eGFR if it is <60ml/min/1.73m2 or state that the eGFR is ≥60ml/min/1.73m2 without providing a precise value. The 95% confidence intervals relative to the value being estimated, true GFR or Cio, are not usually included in the report. The MRDR eGFR is now widely used throughout the world and has replaced the older estimation of Ccr from serum creatinine (the Cockcroft-Gault formula) in many, but not all circumstances (21). Efforts are continuing in the search for improved methods for estimation of GFR, such as use of serum cystatin C levels (25).

The issue of eGFR measurement began to have much greater clinical consequences when the National Kidney Foundation released the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for the evaluation, classification of and staging of CKD in 2002 (20) (Table III). This document and the system it embodied quickly became the reference standard for diagnosing CKD in individuals, in clinical trials and in large scale epidemiological studies for determining the prevalence of CKD. Undoubtedly, the combination of eGFR-MDRD and KDOQI-CKD concepts engendered a great deal of interest in a previously neglected subject. However, the combination of eGFR-MDRD and KDOQI-CKD has conspired to produce several unintended consequences, one of the most important of which relates directly to the issue of the normal decline in GFR with ageing.

The KDOQI-CKD system (Table III) uses an *arbitrary and absolute threshold* for defining Stage 3 and above CKD (<60ml/min/1.73m2). This threshold was selected as it represents about 50% of the young adult values of eGFR. Furthermore, the definition of Stages 3, 4 and 5

TABLE III

The National Kidney Foundation-Kidney Disease Quality Outcomes Initiative (KDOQI) Chronic Kidney Disease (CKD) Classification System (from Reference (20))

Stage of CKD	Kidney Damage*	eGFR**
1	present	>90 ml/min/1.73m2
2	present	60–89 ml/min/1.73m2
3	NA***	30–59 ml/min/1.73m2
4	NA	15–29 ml/min/1.73m2
5	NA	<15 ml/min/1.73m2 (or on dialysis)

* Kidney damage- abnormal urinalysis- hematuria or proteinuria [microalbuminuria or macroalbuminuria], abnormal imaging or abnormal morphology [renal biopsy]- persisting for 3 months or longer.

** eGFR calculated by MDRD equation persisting for 3 months or longer.

*** NA = not applicable.

CKD does not require corroborating evidence of kidney damage (such as proteinuria, abnormal imaging or an abnormal renal biopsy). Thus, Stages 3, 4 and 5 CKD are defined *exclusively* on the basis of absolute thresholds for GFR (MDRD). Anyone with an eGFR <60ml/min/1.73m2 persisting for 3 months or more will be "labeled" as having CKD under this system. We have pointed out elsewhere that this system leads to the *mis-classification* of many elderly, often females, as having CKD when they simply have an eGFR that is less than 60ml/min/1.73m2 (often in the 45–59ml/min/1.73m2 range) but within a "normal" range (>5th percentile) for their age and gender (26). Indeed, population based surveys, such as the National Health and Nutrition Examination Surveys (NHANES) (27), conduced periodically in the USA, have indicated that as many as 13% (or 26,000,000) adults have CKD (60% of these have Stage 3 CKD) based on application of the eGFR-MDRD and KDOQI-CKD criteria to a "representative" sample of the general population. Similar results have been reported from many other countries (28). Not surprisingly, the majority of subjects so diagnosed as having Stage 3 CKD are elderly and female. Over 80% are greater than age 60 years; more than two-thirds have no abnormal proteinuria; and the female:male ratio is 1.27. It is our contention that these observations stem from the lack of either an age- or gender-adjustment in the thresholds of eGFR used to define (and diagnose) CKD. The un-intended consequences are inappropriate labeling of a non-diseased population as having a chronic disease and the attendant unnecessary anxiety and needless evaluations and referrals which often accompany this *mis-diagnosis.* Prevalence estimates for CKD in the general population are also suspect if the KDOQI-CKD and eGFR-MDRD systems are used without recognition of the normal effects of ageing on GFR. It would be anticipated that the prevalence of CKD, so diagnosed, would "track" with the average age and distribution of ages (and thereby the average eGFR) of the population as a whole. For these reasons we have some doubts that there is or ever was an "epidemic" of CKD (27). We also are concerned about the un-intended and undesirable consequences of routine reporting of eGFR every time a serum creatinine is measured (29). This latter process amounts to *de facto* or *"opportunistic"* screening which cannot be justified due to the high likelihood of a "false positive" result when the eGFR values are placed in the context of a flawed system for diagnosis of CKD, based on eGFR. The remedies for this situation are: i) to improve the reliability, accuracy and broad applicability of the eGFR equations; ii) to revise the current classification of CKD to take into account the expected changes in eGFR with age and gender; iii) to add corroborating evidence of

kidney damage (such as proteinuria) when an eGFR of >30ml/min/1.73m2 is identified (irrespective of age or gender). With these changes in the system of CKD assessment and classification it should be possible to use both eGFR and a classification system that is more biologically based and much more aligned with its intended purpose [30].

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DISCUSSION

Berl, Denver: Very nice review. This is a very controversial subject in our field but just for the record, you did use the word "gene." I also have stage III CKD by this criteria, but two comments. Concern has been the increased prevalence of CKD III, and in the college study compared men in 1994, 1999, and 2004 and using the same proportion of people over 60. I think there was an increase from 10 to 13% in CKD prevalence. But I am very sympathetic to your message, because our clinic is flood with consults for people who have GFRs between 50 and 60, and it shows up in the lab data as estimated GFR, CKD stage III, and they don't have proteinuria or other abnormalities and causes all of this anxiety. I think its is important to recognize the point at which an estimated GFR decrease provides a signal of increased cardiovascular risk, and I would like you to address that.

Glassock, Laguna Niguel: Yes, that is actually two points you have made. First of all, I have debated this with Joe Coresh and Andy Levey, and it's my contention that there is not, and never has been, an epidemic of chronic kidney disease (CKD) in the ited

States, and that the growth of the CKD population as described in their surveys is entirely due to the aging of the population and has nothing to do with disease. Secondly in a paper which will be published in about two weeks, the PREVEND study in Gromingen (The Netherlands) has very clearly demonstrated that there is no increased risk of cardiovascular disease, either deaths or events, in stage III CKD if you do not have proteinuria. Proteinuria is the signal of CVD risk. It is not GFR, and I think it's a very solid paper. I hope many of you will take an opportunity to read it, because it puts to rest this notion that GFR is the determinate of risk for CVD.

Weir, Baltimore: Thank you for your comments. I totally agree with you, and to follow up with Tom's comments, you know the issue with the CVD association I think is smart, and if any awareness, it may help us focus on global cardiovascular risk reduction efforts. But I think also if you look at the data, it is really an estimated GFR below 45 when the cardiovascular disease risks start to accrue, and in fairness to Andy he will be publishing in the Annals of Internal Medicine shortly eight new creatinine-based formulae from his current effort—eight new ones which will take into account age and hopefully will provide some more understanding in this regard.

Glassock, Laguna Niguel: Well my purpose today was to try to bring some reality into the sense of eGFR's contribution to our understanding of the dynamics of chronic kidney disease, and it is my personal view that eGFR adds very little to our understanding of this process, but I'm on the defensive side here.

Chapman, Jackson: What happens to renal blood flow during aging, and could this have any consequences in the patients who actually had a rise in serum creatinine?

Glassock, Laguna Niguel: Yes, I didn't show the data, but Davies and Shock reported over 50 years ago, using the classic PAH clearance method of Homer Smith for determining renal plasma flow that does fall, but of course, filtration fraction rises and this is a consequence of the major decline in renal plasma flow, which is probably a reflection of the vacular disease that is progressing in the kidney as individuals age.

Chapman, Jackson: And in the patients who had an increase in renal function with aging, could that be due to hypertrophy of the remaining nephrons?

Glassock, Laguna Niguel: Well global sclerosis occurs progressively, and there is some evidence that the residual nephrons do have some increase in single nephron GFR, However, compensatory hypertrophy is mitigated, in part, by the generalized vascular disease present within the kidney, which tends to modulate the extent of compensatory increases in filtration.