Nutrition, ageing and GFR: is age-associated decline inevitable?

Paul L. Kimmel, Susie Q. Lew and Juan P. Bosch

Division of Renal Diseases and Hypertension, Department of Medicine, George Washington University Medical Center, 2150 Pennsylvania Avenue NW, Washington, DC 20037, USA

Abstract. Due to the paucity of long-term observational data, it is still unclear whether the decreased glomerular filtration rate (GFR) noted in older humans is a result of true changes in renal function over time. The fact that a carefully characterized subpopulation of subjects showed no decrease in GFR over time suggests that the 'physiological decrease' in GFR noted in the elderly is not inevitable. In studies in our patient population, there was a significant correlation between creatinine clearance and nutritional protein intake in elderly patients without renal disease. In our studies, elderly subjects without renal disease who ingested >1 g/kg day of protein had creatinine clearances in the range of 90–100 ml/min/1.73 m², while those with lower protein intakes had lower creatinine clearances. Our studies suggest that GFR is not a fixed function, and that its value may change both over short periods and over decades in humans, with these changes being associated with changes in nutritional protein intake. Low levels of GFR are not necessarily equivalent to a diagnosis of renal disease. Diet must be considered in the assessment of renal function in elderly patients before a diagnosis of renal insufficiency can be made. Decreased GFR is not an inevitable consequence of ageing in humans.

Key words: creatinine clearance; elderly; protein intake; renal function

A recent textbook chapter emphasizes the 'inevitable decline in renal function with ageing' [1]. It is still unclear whether the decreased glomerular filtration rate (GFR) noted in older humans is a result of true changes in renal function over time, because of the paucity of long-term observational data. This paper will highlight considerations regarding change in creatinine clearance in the aged. Creatinine clearance, the clinical approximation of GFR, is defined by the following formula:

\[
\text{creatinine clearance (CC)} = \frac{\text{urinary creatinine excretion}}{\text{plasma creatinine concentration} \times \text{time (T)}}
\]

or rearranging

\[
\frac{\text{total urinary creatinine excretion (UCr)} \times \text{T}}{\text{plasma creatinine concentration (P Cr)} \times \text{CC}} = 1
\]

Cross-sectional studies may be biased because of selective survival in subpopulations, or findings pertinent solely to the particular cohorts. The Baltimore Longitudinal Study of Aging is a notable exception, providing the best data regarding serial changes in GFR and other measures of renal function over time in humans [2–4]. By following 446 participants with five or more serial determinations of creatinine clearance between 1958 and 1981, the investigators demonstrated a linear decrease in GFR with age, both across [2,3] and within populations [3,4]. These subjects were a subset of 1015 volunteers ranging in age from 22 to 97 years at time of study entry. Subjects were characterized as having renal disease, hypertension or oedematous disorders, or as normal. The normal group included subjects with abnormal carbohydrate metabolism, as long as there was no evidence of proteinuria or other urinary abnormalities, and subjects were not treated with diuretics or antihypertensive drugs [4]. The normal subjects comprised 254 of the original 446 volunteers. Circulating creatinine concentrations tended to remain stable over time, although there was a cross-sectional tendency for decline between groups with increasing age [3]. The rate of loss of GFR in this group was 0.75 ml/min/year [4]. Two different patterns, however, were observed in the 446 subjects: (i) progressive decline in renal function over time, typified by negative slopes on a regression equation of creatinine clearance over time, in 65% of subjects; and (ii) positive slopes, suggesting no decline in renal function over time in 35% of subjects; 1.6% of the 446 subjects had a significant increase in creatinine clearance over time.

The putative reasons for this age-related decline in GFR have been considered by various investigators [1,5,6]. Anatomical changes such as small vessel atherosclerotic disease, elements of nephrosclerotic changes and progressive glomerulosclerosis have all been posited as possible causes of such age-related decline [1,5,6]. Dissociation between renal plasma flow and GFR, a physiological 'hyperfiltration of ageing' has also been implicated in the pathogenesis of
age-related decline in renal function \[1,5,6\]. This sequence of physiological events would imply the following variation of equation (1):

$$\text{creatinine clearance} = \frac{(L \text{ or unchanged } U_{Cr}V)/(T \text{ or unchanged } P_{Cr})/(T)}{(1)$$

The fact that a subpopulation, approximately one-third of patients in the Baltimore Longitudinal Study of Aging, however, showed no decrease in GFR over time, or an increase in GFR, suggests that the 'physiological decrease' in GFR noted in the elderly is not inevitable. Nutritional factors have long been associated with short-term changes in renal function. Acute increases in protein intake are associated with a rapid increase in GFR \[7-9\]. These changes are associated with changes in cyclic nucleotide, catecholamine and prostaglandin metabolism \[8,9\]. The possible role of chronic increases in protein intake over time in mediating progressive renal dysfunction in patients with renal disease has been outlined \[10\]. It is possible that long-term high-protein diets are associated with increased glomerular pressures and flows, culminating in progressive renal dysfunction in susceptible subjects, primarily those with pre-existing renal damage \[6,10\].

In order to explore the relationship of nutritional protein intake and renal function in the elderly, Lew and Bosch \[11\] studied elderly patients, without renal disease. Twenty-eight healthy, elderly people were recruited from retirement homes and vegetarian societies. The subjects' mean age was 70.2 years (range 55–88 years). Subjects with a history of renal disease, abnormal urinalyses, urinary protein excretion >100 mg/24 h and hypertension were excluded. Thirty-seven young healthy subjects under the age of 50 years and 33 patients with renal disease served as comparison populations. All patients had evaluation of 24 h urinary excretion of urea and creatinine. Nutritional protein intake was calculated according to the formula of Maroni \textit{et al.} \[12\].

**Relationship between nutritional protein intake and creatinine clearance in normal healthy subjects**

The mean age of the subjects was 31.8 ± 7.9 (SD) years. There was a significant correlation of urinary creatinine and urinary urea excretion in the healthy subjects \((r = 0.8, P < 0.0001)\), over a range of urinary urea excretion from 2 to 17 g/24 h, corresponding to a protein intake of 0.39–1.74 g/kg/24 h. The subjects' mean protein intake was 0.95 ± 0.37 g/kg/day. The subjects' mean creatinine concentration was 0.91 ± 0.19 mg/dl (range 0.5–1.4). Mean creatinine clearance was 97.9 ± 30.2 ml/min/1.73 m² (range 29.5–173.3). Mean urinary creatinine excretion was 1345 ± 549 mg/day (range 391–2545), corresponding to a urinary excretion of 19.6 mg creatinine/kg. A 'normal' GFR of 120 ml/min/1.73 m² corresponded to a protein intake of 1.3 g/kg/day. There was no difference between mean creatinine clearance in men and women. The equation for the line depicted in Figure 1 is creatinine clearance = 64.7 (protein intake) + 36 ml/min/1.73 m².

When the 37 normal subjects were divided into groups with high \((n = 21)\) and low protein intake \((n = 16)\), there were significant differences in BUN, creatinine clearance and creatinine excretion between them, but there were no differences in mean weight, height or plasma creatinine concentration. The differences in creatinine clearance between the groups were accounted for by differences in urinary creatinine excretion.

**Relationship between nutritional protein intake and creatinine clearance in elderly subjects without renal disease**

Creatinine clearance was <120 ml/min/1.73 m² in 27 of the 28 subjects. The subjects' mean plasma creatinine
**Comparison between nutritional protein intake and creatinine clearance in young and elderly subjects without renal disease**

The mean creatinine excretion/nutritional protein intake, and mean creatinine clearance was significantly lower in elderly compared with younger subjects. The equation for the line depicted in Figure 2 is creatinine clearance = 64.1 (protein intake) + 16 ml/min/1.73 m² (r = 0.79, P = 0.0001). Although there was no difference between the slopes of these lines (Figures 1 and 2), the y intercepts are significantly different, suggesting a difference between baseline creatinine clearances in the two groups, but a similar relationship between nutritional protein intake and creatinine clearance in the two groups. As in other studies [3], the differences between creatinine clearances can be accounted for by the differences in level of urinary creatinine excretion. Although there was a relationship between creatinine clearance and nutritional protein intake in both groups, in the young, approximately two-thirds of the change in creatinine clearance was associated with changes in protein intake; in elderly subjects, only 25% of the variance in creatinine clearance was explained by changes in nutritional protein intake. The differences between the intercepts of creatinine clearance and protein intake (20 ml/min, averaged over the mean difference in the subjects’ age, 38.4 years) suggest a change in set point of 0.42 ml/min/1.73 m² year, consistent with the findings of the Baltimore studies.

These findings lend important credence to the longitudinal findings of the Baltimore study. We studied a healthy, well-nourished cohort with a relatively high socioeconomic status. A fairly high proportion of elderly patients do not exhibit a decrease in GFR concomitant with ageing. GFR and nutritional protein intake, however, are associated in healthy elderly patients without renal disease. There are ample data in the USA, especially in urban populations, nutritional protein intake decreases with advancing age. Whether such findings are a concomitant of socioeconomic circumstances or a physiological response to ageing is unknown. However, differences between creatinine clearance in healthy adults of varying ages without renal disease may be a result of different muscle mass and nutritional protein intake. This view implies a different understanding of the relationship between creatinine clearance and creatinine excretion, outlined below.

1. nutritional protein intake → nutritional protein intake → urine creatinine excretion

Our studies suggest GFR is not a fixed function, and that its value may change over short periods, and over decades in humans, prominently associated with changes in nutritional protein intake. Low levels of GFR are not necessarily equivalent to a diagnosis of renal disease. Diet must be considered in the assessment of renal function in elderly patients before a diagnosis of renal insufficiency can be made. The alteration of creatinine excretion by diet also implies that the use of the reciprocal creatinine concentration may not be a valid method of assessing change in GFR over time after a nutritional intervention [13]. In our studies, elderly subjects without renal disease who ingested >1 g/kg/day of protein had creatinine clearances in the range of 90–100 ml/min/1.73 m², while those with lower protein intakes had lower creatinine clearances. The normalization of creatinine clearance for urea excretion may be a useful tool for assessing renal function in both young and elderly subjects with ‘decreased renal function’. Data from the Baltimore study and from our own laboratories lead us to believe that, although elderly subjects tend to have decreased creatinine clearance compared with younger people, decreased GFR is not an inevitable consequence of ageing in normal humans.

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**References**