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Original Article

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Impact of age on glomerular filtration estimates

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Abstract

Background. Glomerular filtration decreases progressively with age in adults. Predictive equation should have proper modelling to adequately account for normal senescence.

Methods. Corrected 24-h creatinine clearances (CCLs) were measured in a cohort of 773 outpatients from 18 to 90 years old. Multiple linear regression was used to model the effect of age on glomerular filtration. Comparisons were made with the simplified MDRD and the MAYO equations. Impact of the derived equation was tested in a second cohort of 7551 patients with normal serum creatinine.

Results. While all equations show declining function with age, our results suggest that the GFR reduction is progressive after the age of 30 and continue to decline steadily after the age of 60. This leads to a convex curve in the multiple regression analysis that is best fitted by an equation including the quadratic term (age^2). In contrast, the MDRD equation produces a faster decrease in early adulthood and a flatter curve after the age of 60 while the MAYO equation produces a more linear effect. MDRD results in the normal range are lower than those estimated by the MAYO equation. These equations, as applied on an independent cohort of 7551 normal outpatients from 18 to 102 years, produce different profile of evolution of GFR with age.

Conclusions. Inclusion of a quadratic term for age in the formula estimating GFR results in better modelling of the natural decline of renal function associated with ageing. Furthermore, as GFR steadily declines after the age of 30, a single cut-off value of GFR normality for all ages leads to underdiagnosis of young adults and over diagnosis of elderly individuals. Guidelines should take into account the observed reduction of kidney function with age in normal population for optimal evaluation of eGFR.

Keywords: age; clearance; creatinine; GFR; glomerular filtration

Introduction

Glomerular filtration rate (GFR) is a fundamental parameter of renal function, often estimated from equations that include creatinine and age as important variables. Although serum creatinine shows little correlation with age in a normal adult population, the creatinine clearance (CCL) decreases significantly with age [1–2]. Nevertheless, a single GFR cut-off of 60 ml/min/1.73 m^2 regardless of age is currently recommended for the definition of chronic kidney disease by the US National Kidney Foundation [3].

Popular equations to estimate GFR (eGFR) include the Cockcroft and Gault [4] (CG) formula and the simplified modified diet in renal disease (MDRD) equation [5,6]. The original CG formula provides an estimate of CCL while the MDRD formula, derived from a large cohort of adults with abnormal kidney function, gives a direct estimate of GFR expressed per 1.73 m^2. In 2003, Rule *et al*. reported a study that included a large group of normal kidney donors evaluated with an iothalamate reference method for GFR estimates [7]. They derived an equation (MAYO) also based on creatinine, age and sex expressing GFR per ml/min/1.73 m^2. Since their study included normal individuals, the MAYO equation has potential for studying the evolution of GFR with age. However, neither the MDRD nor the MAYO-related publication addresses the quality of their models in regard to age.

CCL is frequently used as a clinical tool to evaluate GFR. However, CCL slightly overestimates GFR, mainly due to net tubular secretion of creatinine. It is possible to compensate for the tubular secretion so that the corrected CCL (CCL_C) shows good concordance with calculated GFR. It is expected that eGFR derived from equations should parallel the evolution of CCL_C with age. Our objective was to model the effect of age on measured CCL_C in a cohort of adults (cohort A) with various degrees of renal function and to compare this model to eGFR estimates by the MDRD and MAYO equations. These models were tested in a

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distinct larger cohort of outpatients with normal creatinines to assess the evolution of eGFR by decades.

Subjects and methods

Laboratory methods and eGFR

All serum and urine creatinines were measured in a single laboratory with alkaline picrate reagents and calibrators provided by Beckman Coulter Inc. on an LX-20 analyser similar to Beckman CX-3 that was used in the MDRD study [8]. These analysers have the same creatinine module using kinetic measurements with alkaline picrate reagents. Subjects were instructed verbally for the proper collection of 24-h urine. Measured CCL was normalized to 1.73 m^2 with body surface area estimated from weight and height (Table 1). Our study was done with Beckman calibrators before the restandardization to the IDMS reference method (isotope dilution mass spectrometry). Therefore, we applied the original abbreviated MDRD formula as recommended by the National Kidney Disease Education Program [6,9]. All results for creatinine (Beckman assay) are expressed in μmol/l and the respective equations adjusted accordingly for SI units.

Since a different creatinine assay (Roche Diagnostics, Indianapolis, IN 46250, USA) was used in the development of the MAYO equation, we applied a transformation to ensure comparability of GFR estimates with the MAYO equation. Calibration bias was removed by transforming Beckman values into MAYO equivalent values (Roche assay) with the regression provided by its authors (Cr_{MAYO}) [7]. We then applied the MAYO equation as indicated in Table 1 with Cr_{MAYO} except for values <71 μmol/l (0.8 mg/dl), which were replaced by 71 μmol/l as suggested [7]. Untransformed Beckman values were used to compute CHUQ and MDRD formulas.

Corrected creatinine clearance (CCL_C)

Since CCL overestimates true GFR mainly secondary to net tubular secretion, we applied a correction to better estimate GFR. In the MDRD study, this overestimation was ∼15% [5]. However, it is known that the contribution of tubular secretion increases as the GFR declines [10]. Therefore, a greater correction is necessary for patients with renal insufficiency. Since the MAYO equation covers both normal and abnormal patients similarly to our study group, we used the MAYO equation to study the relationship between eGFR and the CCL over the complete range of renal function. We found that the ratio of CCL over eGFR varies inversely with eGFR. For very low GFR, the creatinine clearance overestimates GFR by ∼40% while the overestimation is ∼10% for a GFR of 120 ml/min/1.73 m^2. The ratio decreases linearly up to 120 ml/min/1.73 m^2 and then stays flat. The following linear relationship was found <120 ml/min/1.73 m^2: CCL/eGFR = 1.41 – 0.00267 eGFR with a significant slope ($P \leq 0.001$). Therefore, we applied this relationship rather than a fixed factor to correct for tubular secretion. By rearranging the terms, we obtain CCl = 1.41 eGFR – 0.00267 $eGFR^2$, which can be solved mathematically giving the following:

$$\text{for CCL} < 120\ \text{ml min}: \quad \text{CCL}_C = (1.41 - \sqrt{1.988 - 0.0107\,\text{CCL}}) \div 0.0053$$

$$\text{for CCL} > 120\ \text{ml/ min}: \quad \text{CCL}_C = 0.9\ \text{CCL}.$$

The corrected clearance CCL_C was then used as a surrogate of measured GFR for study A.

Population setting

Two years of successive data were extracted from the database (CHUQ—Hôtel-Dieu de Québec) to generate two separate cohorts. The hospital provides services to both inpatients and outpatients, including specialized clinics in nephrology. The database also includes results for a general practice outpatient facility that is independent of the hospital.

Study A: modelling of the effect of age on CCL

Cohort A includes 773 adults with measured CCL based on 24-h urine collections. This cohort spans a wide spectrum of kidney function with a significant proportion of subjects (49%) with normal creatinine levels. Most of those subjects were outpatients seen by nephrologists at the hospital. Demographics were available for the calculation of body surface area (BSA) in all cases. Patients with kidney grafts, inpatients and BSA <1.3 m^2 or >2.5 m^2 were excluded. In order to attenuate the inaccuracies of 24-h urine collection, subjects with urine volume <0.6 l or >5.0 l, urinary creatinine <4 or >25 mmol/day were excluded. No attempt was made to exclude patients with chronic kidney disease.

Study B: impact of age modelling in subjects with normal creatinine by decades

Cohort B was selected to represent the general population with normal creatinine values. This cohort includes sequential adult subjects seen at a general practice outpatient facility independent of hospitals. Out of 8119 values,

Table 1. Characteristics of the study populations (mean ± SD)

Origin	Cohort A (outpatients with completed 24-h creatinine clearance)	Cohort B (ambulatory patients from non-hospital based clinic with normal serum creatinine)
Number	773	7551
Age	54.0 ± 16.4 years	55.8 ± 13.4 years
Range	18–90 years	18–102 years
Female	44.6%	52.8%
Body surface area	1.84 ± 0.22 m^2	NA
24-h urinary volume	2.06 ± 0.75 l	NA
24-h urinary creatinine	13.5 ± 4.3 mmol/l	NA
Serum creatinine	143 ± 93 μmol/l	75 ± 13.6 μmol/l
CCL	79.8 ± 42 ml/min/1.73 m^2	NA
CCL_c	67.2 ± 39.8 ml/min/1.73 m^2	

Body surface area = 0.007184 × $\text{weight}^{0.425}$ (kg) × $\text{height}^{0.725}$ (cm).

Table 2. Equations used for eGFR

MDRD exponential format	$eGFR = 186 \times (Cr/88.4)^{-1.154} \times age^{-0.203} \times 0.742$ (if female)
MDRD multiple linear format	$\ln(eGFR) = 10.398 - 1.154 \ln(Cr) - 0.203 \ln(age) - 0.298$ sex
MAYO	$\ln(eGFR) = 1.911 + \frac{464}{Cr} - \frac{16520}{Cr^2} - 0.00686$ age $- 0.205$ sex
CHUQ (this study)	$\ln(eGFR) = 10 - 1.164 \ln(Cr) - 0.000084$ age^2 $- 0.319$ sex

Note: Race as a variable is not included in the MDRD used in this study. The variable sex is 0 for male and 1 for female. For MAYO, if creatinine <71, use 71 μmol/l in the formula (0.8 mg/dl). For natural logarithm format, eGFR can be calculated with $eGFR = e^{\ln(eGFR)}$. For the MDRD and CHUQ formulas with isotope dilution mass spectroscopy traceable creatinine calibration, multiply eGFR results by 0.94.

93% of the serum creatinine measurements were within the laboratory reference ranges so that 7551 normal serum creatinine results were used to estimate various percentiles by decade of age. As the city population has a low proportion (<1%) of black individuals, results were calculated without any special consideration for race.

Statistical analysis

For study A, we conducted analyses with standard multiple linear regression, Pearson correlation coefficients and analysis of residuals to identify the best models predicting CCL_C from creatinine, age and sex. Creatinine and age are continuous variables that could be tested after various transformations. Sex is dichotomous and can only contribute a fix factor in models. Since the relationship of GFR and creatinine is not linear, we tested various transformations of CCLc and creatinine such as logarithmic, exponential, inverse, quadratic, higher order polynomial and the MAYO-type model (Table 2). Similar transformations permitted modelling for age in univariate or multivariate analysis. Linear, quadratic, exponential and other higher order alternatives term for age were considered. Interaction terms were also tested between variables but none were found significant.

To demonstrate the fit quality for the age variable after correction for creatinine and sex, box plots were used (see the legend of Figure 2 for details). This was achieved by plotting the regression residuals of $\ln(CCL_C)$ versus ln(Creatinine) and sex. Improvements in the adjusted coefficient of determination (adj r^2) were used to identify better models. Based on our analysis, a new equation (CHUQ) was derived for the purpose of comparison with MDRD and MAYO (Table 2). For study B, eGFR was estimated with all three equations. Results were analysed by decade to study the evolution of GFR (percentiles estimates) and displayed with box plots. Comparisons between decades were analysed by the Mann–Whitney *U*-test.

Results

Study A: modelling the effect of age on corrected CCL

Characteristics of the cohorts are presented in Table 1. Cohort A includes 428 men and 345 women with a wide range of renal function. Creatinine is by far the most important factor for predicting GFR in this cohort. As in the MDRD study, we found that the logarithm of the CCL_C had an excellent linear relationship (adj $r^2 = 0.82$, $P < 0.0001$) with the logarithm of creatinine [ln(Cr)] (Figure 1). No other transformation gave a better fit, including the Mayo transformation, and thus we kept this log–log relationship in the multivariate analysis. The coefficient found for creatinine in the CHUQ equation (−1.165) is within 1% of the value reported for MDRD (−1.154) as shown in Table 2. We could remove the effect of serum creatinine and sex by analysing the residuals of this regression and study its relationship with age as shown in Figure 2. The residuals isolate the effect of age so that visual assessment is easier. We can observe that the residuals of CCL_C seem quite stable until the age of about 40, then decline progressively, especially above the age of 60. Analysis of residuals by decade showed no difference between decades 1, 2 and 3 with a significant drop at the fourth decade ($P < 0.01$). At first sight, a quadratic term for age (CHUQ) appears to model the convex shape better than a linear (MAYO) or logarithmic (MDRD) term.

In a stepwise forward multiple regression analysis including ln creatinine and sex, the logarithm of age, age and the square of age, only age^2 was selected for the final model as it resulted in the best fit for the residuals ($r^2 = 0.18$, 0.20 and 0.21, respectively, all $P < 0.001$). No other tested modelling for age performed better than age^2. The multiple regression yielded the equation shown in Table 2 (CHUQ equation) with a multiple regression coefficient of $r = 0.932$ ($P < 0.0001$ for each term). The MDRD and MAYO formulas are also indicated for comparison.

Study B: evolution of eGFR with age in subjects with normal creatinine

Since the MDRD, MAYO and CHUQ equations model age in different ways, we wanted to verify independently their impact in an outpatient population from 18 to 102 years

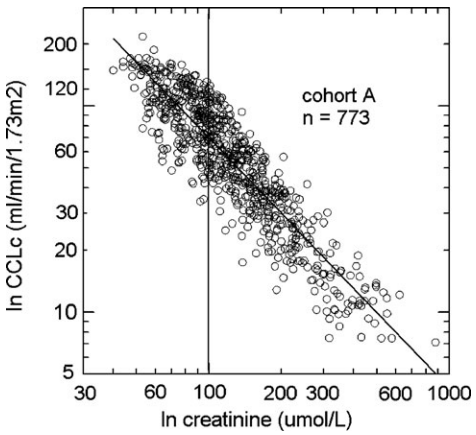

Fig. 1. Log–log relationship between creatinine and corrected creatinine clearance in cohort A. The vertical line indicates a creatinine value of 100 μmol/L, the average upper limits of normals for men and women. Note that the linear relationship holds for creatinines <100 μmol/L on the left.

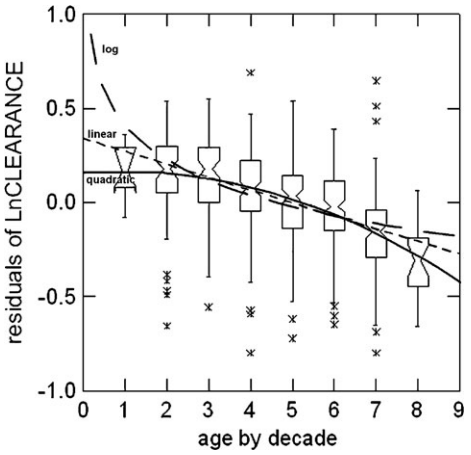

Fig. 2. Evolution of the residuals of ln CCL_C with age, after correction for the effect of creatinine and sex with curve fitting for logarithmic, linear and quadratic models. Note that the box spans the 25th to the 75th percentile of the distribution with a notch indicating the median and its 95% confidence interval. Overlaps of notches between adjacent groups indicate a non-significant difference between medians.

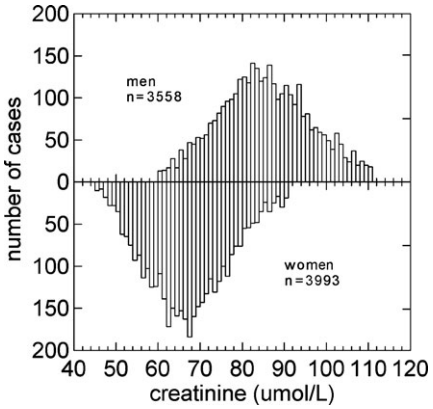

Fig. 3. Distribution of creatinine in cohort B.

(Table 1) with normal creatinines. Figure 3 shows the distribution of creatinine values for both sexes in cohort B. The median creatinines are 67 for women and 84 for men. After the transformation into Cr_{MAYO} values, close to half the women have serum creatinine <71 μmol/l, the minimum value used in the MAYO formula. Figure 4 shows box plots of eGFR estimated by the MDRD, MAYO and CHUQ equations for cohort B.

The eGFR decreases progressively with age in all models, but differences in the evolution with age are quite substantial. The lower boundaries of these distributions are especially noteworthy as they are close to the lower limit of normals (2.5th percentile). The MDRD produces a greater decrease of GFR in early adulthood than in older persons. It tends to stay rather flat after the age of 60. The total drop of the median values is ∼32% from the second decade to the group over the age of 80 with an average decline of ∼5 ml/min/1.73 m^2 per decade. The 2.5th percentiles appear relatively constant above 50 years and are close to the 60 ml/min/1.73 m^2 limit suggested for the classification of chronic kidney disease (Table 3). However, for early adulthood the lower limit of the population is notably >60 as can be seen in Table 3.

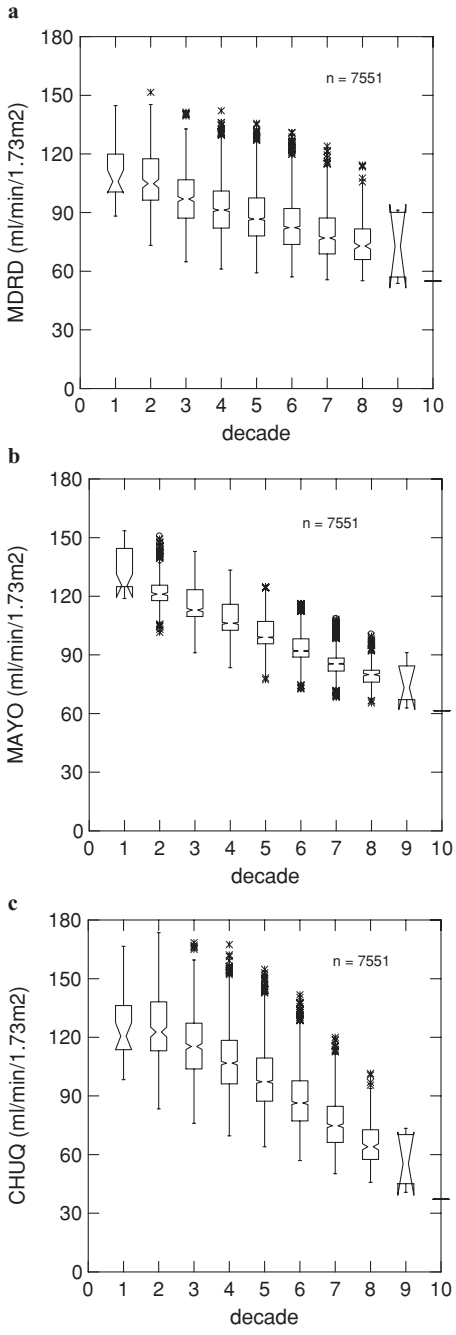

Fig. 4. Distribution of eGFR by decade estimated respectively with (**a**) MDRD, (**b**) MAYO and (**c**) CHUQ in cohort B outpatient population. NB: decade 1 includes only 18–19 years old. NB: readers should be aware that vertical lines in box plots extend approximately to the first and 99th percentile. Also, the scale of the *y*-axis in this figure does not include a logarithmic transformation as in Figure 2, so the convex shape of Figure 2 should become more linear as in (**c**).

Compared to MDRD, the MAYO equation produces higher medians of GFR by >15 ml/min/1.73 m^2 in most decades of cohort B with a more regular drop with advancing age. For MAYO, the percentiles are influenced by the

Table 3. Percentile distributions for creatinine and GFR estimates for both sexes in cohort B

				Women				
Age group	18–29	30–39	40–49	50–59	60–69	70–79	80+	All
Number	170	309	783	1120	895	558	158	3993
Median serum creatinine (μmol/l)	62.5	64	65	66	67	70	71	66
MDRD eGFR								
Perc. 2.5	75.7	71.6	69.0	63.6	60.1	58.4	55.4	60.8
Median	107.0	97.0	90.6	86.2	81.7	75.7	72.7	85.6
Perc. 97.5	141.0	128.4	126.7	121.9	114.1	108.2	105.1	123.7
MAYO eGFR								
Perc. 2.5	106.6	100.0	94.1	86.1	79.2	73.4	67.4	76.7
Median	119.8	110.6	103.7	97.1	90.6	84.3	79.5	95.7
Perc. 97.5	125.3	116.2	108.4	101.3	94.6	88.4	82.6	119
CHUQ eGFR								
Perc. 2.5	87.4	84.2	79.3	70.4	62.3	55.0	45.8	58.1
Median	124.4	114.1	104.6	96.0	84.8	73.1	63.4	93.4
Perc. 97.5	161.9	151.7	147.4	136.1	119.3	104.4	90.6	142.3
				Men				
Age	18–29	30–39	40–49	50–59	60–69	70–79	80+	All
Number	106	291	809	1105	795	362	90	3558
Creatinine median	84	83	83	84	85	87	91	84
MDRD eGFR								
Perc. 2.5	80.3	74.0	71.5	67.1	64.1	61.3	59.8	64.8
Median	101.9	96.9	92.1	87.1	83.1	79.6	73.2	87.5
Perc. 97.5	140.0	127.2	121.1	122.2	115.8	109.4	98.8	121.7
MAYO eGFR								
Perc. 2.5	105.3	96.8	91.7	84.2	77.2	71.2	67.6	76.9
Median	131.3	123.7	115.8	107.2	98.9	92.1	82.1	106.3
Perc. 97.5	151.8	138.6	130.7	122.9	114.8	106.3	98.5	133.9
CHUQ eGFR								
Perc. 2.5	94.4	88.5	83.4	75.4	67.5	59.2	53.5	63.3
Median	120.6	116.4	108.7	98.7	87.8	77.9	64.3	98
Perc. 97.5	164.1	153.1	143.5	138.6	124.0	108.8	90.3	142

minimum value of 71 μmol/l used in the calculation. This tends to artificially blunt the span of eGFR observed in each group, especially for women. The total drop in the median values from the first group to the last group is ∼35% for women and 38% for men. The average drop of eGFR is around 7 ml/min/1.73 m^2 per decade. Before the age of 50, the lower limit is >90 ml/min/1.73 m^2 and it decreases to ∼67 for the oldest group.

Finally, the CHUQ formula shows a more stable GFR for the first three decades and then a steady decline without any plateau above the age of 60. The rate of declining function is ∼10 ml/min/1.73 m^2 per decade and seems rather constant after the age of 30. The 2.5th percentile is lower in women than in men for all groups as for the MDRD formula. However, the fall in the median and the lower percentiles is more pronounced overtime than with the MDRD. For women, the 2.5th percentile decreases from 87.4 to 45.8 and for men from 94.4 to 53.5 ml/min/1.73 m^2. Especially in this model, a fix cut-off for identifying kidney malfunction would lead to poor performance in terms of sensitivity or specificity depending on the age groups. It is quite clear that age modelling markedly influence the apparent rate of GFR decline by decade in subjects with normal creatinines, with respective average values (although not linear) of 5, 7 and 10 ml/min/1.73 for MDRD, MAYO and CHUQ.

Discussion

Equations use to estimate GFR in adults should properly model the natural decline of kidney function with age. Our study demonstrates that inclusion of a quadratic term for age (age^2) in a new equation (CHUQ) results in better modelling of normal kidney senescence. This study also demonstrates that normal eGFR declines with ageing and that definition of 'normal' kidney function based on a single value can be misleading as CKD could be underdiagnosed among young individuals while overdiagnosed in very old ones.

Validity of our model

Serum creatinine is the main predictor of GFR. Our data show that the log–log relationship between GFR and plasma creatinine as applied in the MDRD formula appears to be an excellent choice to linearize this relationship. Furthermore, our study shows that this relationship can be extended into the normal range (Figure 1), which is an important consideration as the MDRD formula was developed from patients with renal insufficiency. The serum concentration of creatinine is relatively stable in older individuals as a result of proportionate reduction in both the clearance and the production of creatinine [11]. One can argue that the

methodology of our study is poor due to correction of an imprecise method to estimate GFR (cCCL). We agree that urine collection is not a gold standard method to assess GFR, but we believe that the size of the cohort partly counterbalances the imprecision of the method. It is reassuring to note that the coefficients found for creatinine and sex in our regression statistics (CHUQ equation) are very close to those of the MDRD equation (Table 2). This supports the validity of our corrected creatinine clearance as a reasonable surrogate of GFR.

In the absence of urine collection, sex, age and race can be viewed as a way to estimate the numerator of the clearance UV/P or the quantity of creatinine excreted per 1.73 m^2. However, sex and ethnicity are dichotomous variables that can only provide a fix factor for the respective sub-groups. Age is the only continuous variable that can modulate estimates of the numerator. Thus, the age variable should be able to fit the physiologic decline of creatinine production. Our study is the first to address this modelling in a formal way.

Cockcroft and Gault and others had already recognized the decreased excretion of creatinine with age and suggested a causal relationship with decreasing muscle mass [4]. They described the negative linear relationship between creatinine excretion per 1.73 m^2 and age [4]. However, when using the logarithm of creatinine excretion, it can be demonstrated mathematically that the relationship becomes convex instead of linear. The residuals of $\ln(CCL_C)$ after correction for creatinine and sex are thus expected to give a convex curvature when plotted against age. Our data (Figure 2) are compatible with such a curvature that reflects the declining creatinine excretion in older age groups, especially after the sixth decade. In contrast, relative stability is supported by nearly identical medians of the residuals per decades 1, 2 and 3 (Figure 2). A simple quadratic term (age^2) could fit this curvature satisfactorily as used in the CHUQ model.

The use of the term (age^2) provided a slightly better fit than a straight line (term age) as used in the MAYO equation (Figure 2). We can certainly exclude a model that would suggest a steeper decline in early adulthood and more stability later in life as the use of logarithm of age has done in the MDRD equation. In our view, the apparent flattening of GFR in older groups with MDRD is more related to a model artefact than a true relative stability in the evolution of GFR. We can see the consequences on GFR estimates of the three models (natural logarithm of age, age and age^2) by considering Figure 4 and the percentiles as shown in Table 3.

Modelling eGFR and age

One advantage of GFR estimation is to highlight the physiologic decline of renal function with age. This decline was described as early as 1950 by Davies and Shock [1]. Most studies used creatinine clearance or other direct measures of GFR with exogenous compounds, like inulin, iothalamate, EDTA and iohexol. Similar trends were reported in either case [12–13]. In the large third US National Health and Nutrition Examination Survey, the decrease of creatinine clearance was estimated as 8 ml/min per decade in adults [14].

Verhave *et al*. reported a study on 8446 subjects from the city of Groningen in the Netherlands [15]. Measured creatinine clearance showed a parabolic curve over age with an acceleration of clearance decline above 50 years in both males and females. Similarly, Back *et al*. assessed iohexol clearance in healthy male volunteers ranging from 21 to 77 years [16]. They found a negative correlation above the age of 50 years (−12 ml/min/decade) but no dependence on age for younger subjects. A meta-analysis of eight normal value studies using inulin or radioactive EDTA showed a decline of 4 ml/min/1.73 m^2 up to 50 years and a decline of 10 ml/min/1.73 m^2 after that age [17]. Grewal *et al*. reported their experience in 428 kidney donors evaluated with radioactive chromium EDTA. GFR remained constant until the age of 40 years and then declined at a rate of 9.1 ml/min/1.73 m^2 per decade [18]. In agreement with the aforementioned studies, our model results in relative stable GFR up to the age of 30, followed by a slow decline.

However, not all authors agree on the steeper slope in older age groups. Rule *et al*. reviewed the records of 365 carefully selected potential kidney donors with an average age of 41 ± 11.4 (SD) [19]. GFR was measured as an iothalamate clearance and declined on average by 4.9 ml/min/1.73 m^2 per decade. These authors argue for a linear constant drop in all age groups. They reported a decline of 3.5 ml/min/1.73 m^2 up to the age of 50 years and 5.5 ml/min/1.73 m^2 after the age of 50 years, a non-significant difference. Finally, an interesting study was reported by Fehrman *et al*. who performed iohexol clearance in 52 healthy persons aged 70–110 years [20]. The average GFR was 67.7 ± 10.8 ml/min/1.73 m^2 with an estimated decline of 10.5 ml/min per decade. None of the elderly over the age of 90 years had a GFR over 70 ml/min/1.73 m^2. Our own data suggest a regular decrease of GFR from ∼120 ml/min/1.73 m^2 in early adulthood down to ∼60 ml/min/1.73 m^2 in the 80s with a continuous trend over 50 years. The relative flattening of the MDRD after 50 years does not seems to follow properly the physiologic impact of age secondary to the use of the logarithmic transformation in that model. Recently, Björk *et al*. reported that MDRD overestimates GFR by 14% in women and by 22% in men aged 80 years or older [21]. The observed usual decrease of GFR in subjects with normal creatinine has potential implications for patients as it may also apply to patients with different levels of 'stable CKD'. Then a decrease of GFR would also be expected in CKD patients in spite of disease inactivity.

Cohort B is a cross-sectional population that clearly shows differences in GFR in various decade groups. A cautionary note is, however, necessary as it may be challenging to identify true normal individuals, especially in an older population. It could be difficult to distinguish the effect of 'normal physiologic ageing' from pathologic processes like atherosclerosis and hypertension [2]. Therefore, the decrease in GFR may be preventable to a large extent. However, we would argue that the cohort B is representative of ambulatory individuals considered 'normal' by today's standards. With more aggressive preventive measures,

it could be conceived that GFR could be maintained. A longitudinal extended study over many years with intensive follow-up optimizing blood pressure control and other preventive measures might differentiate senescence from decline secondary to vascular sclerosis.

Furthermore, serum creatinine in the low normal range is particularly influenced by imprecision and interferences so that normal eGFR, especially over 120 ml/min/1.73 m^2 has poor accuracy. The MDRD study itself did not include patients with normal function. This has led to many restrictions by professional organizations on eGFR reporting for eGFR >60 ml/min/1.73 m^2. Another limitation of our study is the reliance on corrected creatinine clearance, as we did not perform exogenous GFR measurements. However, our data are quite consistent with the literature on both the evolution of creatinine excretion with age and the estimations of GFR [22–23]. Also, as our study has been derived almost exclusively from an adult Caucasian population, our data may not apply to black and other populations.

Several conclusions can be derived from our study. (1) eGFR decreases normally with age. (2) Our data suggest that it is possible to extend the log–log relationship, as used in the MDRD formula, between serum creatinine and GFR into the normal range. (3) The MDRD equation gives lower eGFR in normal individuals compared with the MAYO formula. (4) eGFR profiles are significantly influenced by the model used for age in the equation. (5) The square of age as used in the CHUQ equation provides a better fit to describe the evolution of ln(GFR) with age. (6) A single cut-off of 60 ml/min/1.73 m^2 for all ages does not give adequate sensitivity for early adulthood and could miss significant renal abnormalities in that group. The same cut-off could over diagnose renal problems in the elderly. (7) The fitting model used for age influences significantly age-adjusted reference ranges.

To confirm our result a quadratic model for age could be applied easily to the MDRD and MAYO data. Future large cohort studies should study the value of their equation into the normal range and fit appropriately the impact of age. Age-adjusted reference ranges could be developed for the equation used. Another possibility would be the development of age-specific guidelines to clinicians. The full potential of the eGFR could then be exploited with its own relevance and limitation for the diagnosis of early renal disease.

Conflict of interest statement. None declared.

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