Estimating glomerular filtration rate in the general population:
the second Health Survey of Nord-Trondelag (HUNT II)

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Abstract

Background. Guidelines recommend the modification of diet in the renal disease (MDRD) formula or the Cockcroft–Gault formula for estimating the glomerular filtration rate (GFR). However, there is an ongoing discussion whether the MDRD formula should be used in the general population as several studies have found a large underestimation of its GFR estimates.

Methods. In this study, 1029 low-risk subjects, eligible for kidney donation according to internationally accepted criteria were selected from the population-based second Health Survey of Nord-Trondelag (HUNT II). Serum creatinine values traceable to isotope dilution mass spectrometry were used with the re-expressed MDRD formula recently published. The 2.5th, 50th and 97.5th percentiles of GFR by age were calculated and compared to reference values from the literature, which are based on GFR measured with gold standard methods in potential kidney donors.

Results. The difference between the 50th percentiles for MDRD estimates and measured GFR in the literature was small and constant over age: +0.5 ml/min/1.73 m² at age 20 and −2.0 ml/min/1.73 m² at age 80. Bias for Cockcroft–Gault estimates varied from 0.0 ml/min/1.73 m² to −21.4 ml/min/1.73 m². Other formulae also had a too steep age correction, and bias among the elderly varied from −10 to −30 ml/min/1.73 m². Hence, 30–80% of the general population above age 60 had GFR estimates below their age-specific 2.5th percentile of normal kidney function, while the MDRD formula was much more conservative (13.3%).

Conclusion. The MDRD formula gave nearly unbiased estimates for normal GFR. All other formulae tested had, especially in the elderly, a much larger negative bias and cannot be recommended for use in the general population.

Keywords: chronic kidney disease; Cockcroft–Gault; general population; glomerular filtration rate; MDRD formula

Introduction

The US K/DOQI guidelines and European Best Practice guidelines state that kidney function should be assessed with glomerular filtration rate (GFR) estimating formulae, such as Cockcroft–Gault or the modification of diet in renal disease (MDRD) study formula, instead of relying on serum creatinine alone [1,2]. The MDRD formula was derived from a large group of Chronic Kidney Disease (CKD) patients using renal clearance of iothalamate as reference method [3]. The methodological foundation should therefore be very strong, and the formula is generally accepted to perform well at GFR levels below 60 ml/min/1.73 m². However, there is an ongoing discussion whether the formula should be used in the general population where most subjects have a GFR above this level [4].

Calibration of serum creatinine measurements is an important aspect that often has been overlooked in previous studies. Most laboratories report values that deviate substantially from reference methods like isotope dilution mass spectrometry (IDMS). In the MDRD study, serum creatinine was analysed with a Jaffé method giving unusually low values, and thereby a potential for underestimation of GFR in most other laboratories [5,6]. Rule et al. [7] studied 580 kidney donors and found that the MDRD formula underestimated GFR with 29 ml/min/1.73 m². Poggio et al. [8]...
also studied the performance of the formula in potential kidney donors and found a bias of −9 ml/min/1.73 m². Interestingly, neither of the two studies paid sufficient attention to the problems arising from inter-laboratory calibration differences. A new re-expressed version of the four-variable MDRD formula for use with IDMS traceable serum creatinine values was recently published to overcome these problems [9].

GFR measured with reference methods in potential kidney donors can be considered to show the normal GFR range and its change with age. GFR estimated with a creatinine-based formula in a similar group from the general population should give similar results. The second Health Survey of Nord-Trøndelag County (HUNT II) is a large population-based study conducted in Norway with a high participation rate. Information is available for proper recalibration of serum creatinine values and also for accurately defining a subpopulation eligible for kidney donation based on repeated measurements of urine albumin, blood pressure, general health, medical history, etc. The aim of our study was to evaluate if GFR, estimated with the new MDRD formula, as well as other frequently used formulae, in such a population-based low-risk group, is in accordance with established reference range of normal kidney function.

Material and methods

Study sample and design for HUNT II study

During the years 1995–97, a large-scale general health survey was conducted in Nord-Trøndelag County, Norway. Inhabitants of the county (n = 92 703) aged >20 were invited to participate in the study, and 70.1% responded. The survey comprised an extensive questionnaire and a brief clinical examination in addition to several clinical chemistry analyses. The population in Nord-Trøndelag is stable (net out-migration of 0.3% per year) and ethnically homogeneous (97% Caucasians). Nord-Trøndelag County is located in the middle of Norway, and it is a representative for Norway regarding geography, economy, industry, age distribution, morbidity and mortality [10]. All participants signed an informed consent, and additional permissions were obtained from the Regional Ethics Review Committee and the National Data Inspectorate. A more detailed description on objectives, contents, methods and participation in HUNT II has been given elsewhere [11].

Clinical and laboratory investigations

The clinical examination included measurement of height, weight and blood pressure. Three consecutive standardized blood pressure measurements were recorded in the sitting position at 1 min intervals using an automatic oscillometric method (Dinamap 845XT; Criticon). Blood was drawn, often in the non-fasting state, from all the participants, and fresh serum and urine samples were analysed at the Central Laboratory of Levanger Hospital on a Hitachi 911 auto-analysers within 2 days. Glucose was measured by means of an enzymatic hexokinase method, total and HDL cholesterol by means of an enzymatic calorimetric cholesterolesterase method. Day-to-day coefficients of variation were 1–2% for all analyses. Urine samples were from three consecutive mornings, and those reporting urine infection during the previous week or menstruation at the time of collection were excluded. Urine albumin was measured by an immunoturbidimetric method (anti-human serum albumin from Dako AS, Denmark) and urine creatinine was measured with the Jaffé method. The albumin-to-creatinine ratio (ACR) was used as an expression for urine albumin excretion. Two or three ACR determinations ranging 2–30 mg/mmol for men and 3–40 mg/mmol for women were classified as persistent microalbuminuria. Subjects with one or more samples above the microalbuminuric range were classified as macroalbuminuric.

GFR estimation

Serum creatinine was analysed on fresh serum in 1995–97 using a Jaffé method with sample blank (Roche Diagnostics, Mannheim, Germany). This was a kinetic Jaffé method without deproteinization based on the test principle that creatinine forms a coloured complex with picrate in alkaline solution. The same method was used until 2003 when 200 samples from the HUNT II study were thawed and reanalysed to ensure stability of methods over time. Mean difference was 0.018 mg/dl (1.6 μmol/l) and r² was 0.994 (Pearson correlation coefficient). The laboratory then switched to an enzymatic creatinine test (CREA Plus, Roche Diagnostics, Mannheim, Germany), and a thorough correlation between the old and the new method was established.

Formulæ used for estimating GFR are given in Table 1. For the MDRD formula, we used two different versions, and serum creatinine values were recalibrated to the same level as used when developing the MDRD formula:

(i) New re-expressed four-variable formula for IDMS traceable serum creatinine values:

\[
GFR = 175 \times [s-creatinine (mg/dl)]^{-1.154} \times \text{age}^{-0.203} \\
(x \times 0.742 \text{ for women}) (x \times 1.21 \text{ for blacks}) [9].
\]

Serum creatinine (mg/dl) = −0.31 + 1.11
\times serum creatinine

This recalibration of Jaffé based creatinine values to the Roche enzymatic method provided IDMS-traceable values. This enzymatic method was the same as used for recalibrating the original MDRD creatinine values to the IDMS level [9], and the method was also found to be comparable to the IDMS level in the Nordic Reference Interval Project [13]

(ii) Original four-variable formula:

\[
GFR = 186.3 \times (s-creatinine)^{-1.154} \times \text{age}^{-0.203} \\
(x \times 0.742 \text{ for women}) \times 1.21 \text{ for blacks}) [12].
\]

Serum creatinine (mg/dl) = −0.21 + 1.08
\times serum creatinine [6].

This recalibration previously provided unbiased estimates of measured GFR by EDTA plasma clearance in a sample of
Table 1. Formulae used for estimating kidney functions in females and males

<table>
<thead>
<tr>
<th>Formula</th>
<th>Females Formula</th>
<th>Males Formula</th>
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<tbody>
<tr>
<td>New MDRD [9]</td>
<td>$F: 175 \times sCr^{-1.154} \times \text{age}^{-0.203} \times 0.742$</td>
<td>$M: 175 \times sCr^{-1.154} \times \text{age}^{-0.203}$</td>
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<tr>
<td>Original MDRD [12]</td>
<td>$F: 186.3 \times sCr^{-1.154} \times \text{age}^{-0.203} \times 0.742$</td>
<td>$M: 186.3 \times sCr^{-1.154} \times \text{age}^{-0.203}$</td>
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<td>Cockcroft and Gault [21]$^a$</td>
<td>$F: (140 - \text{age})/sCr \times (\text{weight}/72) \times 0.85$</td>
<td>$M: (140 - \text{age})/sCr \times (\text{weight}/72)$</td>
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<td>Jelliffe and Jelliffe [22]</td>
<td>$F: [98 - (0.8 \times (\text{age} - 20))]/sCr \times 0.90$</td>
<td>$M: [98 - (0.8 \times (\text{age} - 20))]/sCr$</td>
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<tr>
<td>Salazar and Corcoran [23]$^a$</td>
<td>$F: (140 - \text{age}) \times [(0.287 \times \text{weight}) + (9.74 \times \text{height}^2)]/(60 \times sCr)$</td>
<td>$M: (137 - \text{age}) \times [(0.285 \times \text{weight}) + (12.1 \times \text{height}^2)]/(51 \times sCr)$</td>
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<td>Mawer et al. [24]$^a$</td>
<td>$F: \text{weight} \times [25.3 - (0.175 \times \text{age})]/[1 - (0.03 \times sCr)][(14.4 \times sCr) \times (\text{weight})]$</td>
<td>$M: \text{weight} \times [29.3 - (0.203 \times \text{age})]/[1 - (0.03 \times sCr)][(14.4 \times sCr) \times (\text{weight})]$</td>
</tr>
<tr>
<td>Bjornsson [25]$^a$</td>
<td>$F: [25 - (0.175 \times \text{age})] \times \text{weight} \times 0.07/sCr$</td>
<td>$M: [27 - (0.173 \times \text{age})] \times \text{weight} \times 0.07/sCr$</td>
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<tr>
<td>Gates [26]</td>
<td>$F: (60 \times sCr^{-1.11}) + (56 - \text{age}) \times (0.3 \times sCr^{-1.11})$</td>
<td>$M: (89.4 \times sCr^{-1.11}) + (55 - \text{age}) \times (0.447 \times sCr^{-1.11})$</td>
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<tr>
<td>Wright et al. [27]$^a$</td>
<td>$F: (6580 \times 38.8 \times \text{age}) \times \text{BSA} \times 0.832/(sCr \times 88.4)$</td>
<td>$M: (6580 \times 38.8 \times \text{age}) \times \text{BSA} \times 0.832/(sCr \times 88.4)$</td>
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Serum creatinine (sCr) is measured as mg/dl in all the formulae.
$^a$Formulae with results expressed as millilitre per minute were adjusted to a body surface area (BSA) of 1.73 m$^2$ by multiplying the estimate by 1.73/BSA.

215 kidney patients and potential kidney donors at St Olav Hospital [6]. We also checked for calibration differences between Levanger Hospital and St Olav University Hospital: both the laboratories used the same kinetic Jaffé method with sample blank on Hitachi analysers with reagents from Roche during the entire period 1995–2003. Results from 64 monthly external quality controls (Lab Quality, Finland) were available, and there were no significant differences between the laboratories (mean difference 1.1 mmol/l, 95% CI –1.0–3.2 mmol/l).

Defining a subgroup eligible for kidney donation

Subjects from a 5% random sample of HUNT II participants ($n = 3270$) were evaluated, as these had undergone extensive testing for albinuria. Subjects were excluded, according to internationally accepted criteria for kidney donation, excluded if any of the following were found [14]: (i) macroalbuminuria defined as albumin/creatinine ratio $>30$ mg/mmol for men and $>40$ mg/mmol for women; (ii) diabetes mellitus defined as previously known diabetes or blood glucose $\geq 11.2$ mmol/l, two or more hours after the last meal; (iii) hypertension defined as $\geq 140$ mmHg systolic or $\geq 90$ mmHg diastolic or taking antihypertensive medication; (iv) prior cardiovascular disease (CVD) defined as angina pectoris, myocardial infarction or stroke; (v) serum creatinine above normal range (115 mmol/l for women and 133 mmol/l for men); (vi) malignancy; (vii) body mass index (BMI) $>35$ kg/m$^2$; (viii) not reporting good or excellent general health.

Defining normal GFR level using published data from potential kidney donors

We searched the literature for studies reporting individually measured GFR values and age in subjects evaluated for live kidney donation. Reference methods for measuring GFR based on renal or plasma clearance of injected radioisotopes or contrast agents (EDTA, iothalamate, inulin, etc.) were considered. We recorded age and measured GFR from these studies into a common database. Similar methods for estimating percentiles of GFR in this pooled database as well as for the HUNT data were used: a linear regression model was fit to the log-transformed GFR values, estimating the mean and standard deviation of log(GFR) as $b_0 + b_1 \times \text{age} + s$, respectively. The appropriateness of log transforming was confirmed by Q–Q plots. The 2.5, 50 (median) and 97.5th percentile of GFR for a given age were estimated as $\exp(b_0 + b_1 \times \text{age} + k \times s)$ with $k$ as $-1.96$, 0, and $+1.96$, respectively.

Results

We searched the literature and found four previous studies reporting individual GFR values by age: Grewal and Blake [15], Rule et al. [16], Hamilton et al. [17] and Davies and Shock [18]. We were able to regenerate 97.5, 99.2, 95.0 and 100% of the reported data, respectively. Figure 1 shows that GFR values measured with reference methods in these 1040 potential kidney donors ranged from 31 to 162 ml/min/1.73 m$^2$. Median measured GFR fell from 112.5 ml/min/1.73 m$^2$ at age 20 to 78.5 ml/min/1.73 m$^2$ at age 80. Correspondingly, the 2.5th percentile fell from 82.5 ml/min/1.73 m$^2$ to 57.5 ml/min/1.73 m$^2$.

From the 65 186 participants in the HUNT II study, 3 270 were selected randomly for urine collection. Of these, we identified 1 029 low risk subjects aged 20–83 who would have been eligible for kidney donation (Figure 2). By definition, none of them had risk factors such as hypertension, diabetes mellitus or prior CVD, while the prevalence of these risk factors in the...
The general population was 43.1, 3.4, and 7.9%, respectively. Other characteristics of the participants are given in Table 2.

Figure 3 shows individual GFR values estimated with the new re-expressed MDRD formula in the 1029 potential kidney donors from the HUNT II study. Estimated GFR ranged from 49 to 182 ml/min/1.73 m². Calculated 2.5th, 50th, and 97.5th percentiles are also shown. The 50th percentile for estimated GFR fell from 113.0 ml/min/1.73 m² at age 20 to 76.5 ml/min/1.73 m² at age 80. Correspondingly, the 2.5th percentile fell from 79.5 ml/min/1.73 m² to 54.0 ml/min/1.73 m².

Figure 4A shows that the difference between GFR, estimated with the new re-expressed MDRD formula using directly calibrated creatinine values and measured GFR, was small at all GFR levels and constant throughout the age range: for the 50th percentile, bias ranged from +0.5 ml/min/1.73 m² at age 20 to -2.0 ml/min/1.73 m² at age 80. For the 2.5th percentile, bias ranged from -3.0 to -3.5 ml/min/1.73 m². Using similar analysis, Figure 4B shows that GFR estimated with Cockcroft–Gault formula was correct among the young, but the age correction was too steep. For the 50th percentile, bias varied from 0 at age 20 to -21 ml/min/1.73 m² at age 80. For the 2.5th percentile, bias varied from +5 to -13 ml/min/1.73 m². Corresponding results using other well-known formulae for estimating GFR are given in Table 3. The original four-variable MDRD formula with indirectly calibrated GFR values had a small and constant negative bias (-4.5 ml/min/1.73 m² for the 50th percentile). The Gates formula had a large negative bias at all GFR levels and all ages. The remaining formulae had an age correction that was too steep, so that most overestimated GFR in the young and underestimated GFR in the elderly. We also report the results if unadjusted serum creatinine values were used with the original four-variable MDRD formula. This gave a large bias of approximately -20 ml/min/1.73 m² at all ages.
Bias for the 2.5th percentile ranged from −2 to −17 ml/min/1.73 m² at age 80 using various formulae. As a consequence, many subjects would have been classified as having an abnormally low GFR for their age, i.e. below the 2.5th percentile for reference methods, when applying these formulae on the general population. Figure 5 shows that the new re-expressed MDRD formula estimated 7.1% of the total adult population to have an abnormally low GFR, and the Cockcroft–Gault formula estimated 18.6%. Among subjects over age 60, the corresponding results were 13.3 and 48.8%. The other formulae estimated that 30–80% of the latter group have low GFR. The correct prevalence of low GFR is not known, but the new MDRD formula clearly gave the most conservative estimate.

The prevalence of CKD stage 3−5 (GFR <60 ml/min/1.73 m²) was also calculated using various formulae: 4.7% when using the new MDRD formula (3064 cases among 65 193 HUNT II participants), 14.6% with Cockcroft–Gault, 25.1% with Jelliffe, and 10−15% with the other formulae.

**Discussion**

We compared the estimated GFR in healthy low-risk subjects eligible for kidney donation from the HUNT II study to the measured GFR in potential kidney donors pooled from the literature. The new re-expressed MDRD formula gave unbiased estimates of normal
GFR (+0.5 ml/min/1.73 m² at age 20 and −2 ml/min/1.73 m² at age 80). Other formulae tested were much more biased, and all had a large negative bias among the elderly. Median GFR estimated with the Cockcroft–Gault formula was unbiased among subjects 20 years old, but the bias increased to −21 ml/min/1.73 m² at age 80. We found that 49% of the general population above the age of 60 would have an estimated
GFR below their age-specific 2.5th percentile using the Cockcroft–Gault formula, while the new MDRD formula gave a much more conservative estimate of 13.3%.

Several large studies have recently concluded that using the MDRD formula in healthy subjects is problematic. Rule et al. [7] found that the formula underestimated GFR by 29 ml/min/1.73 m² in kidney donors, and Poggio et al. [8] found a bias of −9 ml/min/1.73 m². Both were aware of the serum creatinine calibration problems but did not solve the problem sufficiently. Rule et al. mentioned in the discussion that a recalibration similar to Coresh et al. [5] would have reduced the bias to −4 ml/min/1.73 m². Poggio restricted his study to the years after 1996 as the bias in the preceding years was even larger (−20 to 30 ml/min/1.73 m²). Froissart et al. [19] solved the problem elegantly by ultrafiltrating plasma through a 20 kDa cut-off membrane before measurement and thereby, eliminated the problem of non-creatine chromogens. In their study of 1,044 persons with GFR above 60 ml/min/1.73 m², they found a bias of only −3.3 ml/min/1.73 m².

The relationship between serum creatinine, muscle mass and age is problematic and has enforced the need for formulae to estimate GFR. However, the accuracy of different formulae in the young vs the old have seldom been reported. Froissart et al. [19] found that the Cockcroft–Gault formula changed from a slight positive bias at age under 65 (+3 ml/min/1.73 m²) to a significant negative bias at age over 65 (−13 ml/min/1.73 m²). The MDRD formula had a bias that was similar among younger and older subjects. Cirillo et al. [20] also found a linear trend for relative error in

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<td>and Jelliffe</td>
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<tr>
<td>Gates [26]</td>
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<td>−16.7</td>
<td>−6.9</td>
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<td>−16.0</td>
<td>−5.5</td>
<td>−14.2</td>
<td>−27.6</td>
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Bias is calculated as the difference between estimated GFR and measured GFR (ml/min/1.73 m²). Negative numbers represent an underestimation of GFR. Positive numbers represent an overestimation of GFR.

*Using sCr values not calibrated to the same level as in the MDRD study.

**Table 3. Bias for 2.5th, 50th and 97.5th percentile when estimating GFR with various formulae in subjects aged 20 and 80 years**

**Fig. 5.** Percentage of the general population found to have an estimated GFR below their age-specific 2.5th percentile of normal kidney function.
Cockcroft–Gault estimates stratified by age (+5% at ages 18–24, –36% at ages 65–88). The MDRD formula had, without recalibration of serum creatinine values, a constant relative error of –11% in their study. This is well in accordance with our results, and most other formulae tested in our study also showed a bias that changed with age.

When the problems with interlaboratory calibration differences for serum creatinine are properly taken care of, the MDRD formula seems to be nearly unbiased and without the problem of underestimating GFR among the elderly hampering all other formulae. The re-expressed four-variable MDRD equation, which was published very recently, has coefficients appropriate for use with a zero-biased creatinine method [9]. This will facilitate correct calibration of serum creatinine values and thereby, bring implementation of formula based GFR estimation several steps forward. However, the accuracy of the MDRD is only moderate among subjects with normal or near normal GFR. Errors of ±15–30% are not uncommon [6,8,19], so direct measurement of GFR with a reference technique should be considered if high accuracy is needed.

The large underestimation of GFR in older subjects using the Cockcroft–Gault formula is now increasingly documented [19,20]. As CKD is most prevalent among the elderly, using this formula will introduce large errors in epidemiological research, and the underestimation will also be of clinical importance for many patients. The recommendation of the Cockcroft–Gault formula found in most international CKD guidelines should therefore be reconsidered.

The weakness of the current study is the indirect comparison of estimated and measured GFR. However, the optimal alternative, which means measuring GFR with reference technique in a large number of subjects from the general population, is unlikely to be done. The strength or our study is the large number of subjects with an age ranging from 20 to 83 years. Due to the very comprehensive HUNT II database, we were able to ensure that all of them really were eligible for kidney donation according to internationally accepted criteria. Our indirect calibration of serum creatinine for the original four-variable MDRD formula has been well described and has previously been shown to give unbiased estimates when using the MDRD formula [6]. However, correct calibration of the creatinine values is now more straightforward with the new MDRD formula. Our gold standard, i.e. the reference limits of normal GFR by age, should also be optimal as we have pooled individual results from available studies. We therefore, feel that our results have a solid methodological basis and can be generalized.

In summary, when using IDMS traceable serum creatinine values and the re-expressed MDRD formula, GFR estimates from the general population were nearly unbiased at all ages (+0.5 to –2.0 ml/min/1.73 m²). The Cockcroft–Gault formula had a large negative bias among the elderly (–21 ml/min/1.73 m²), and similar results were found in all other formulae tested (–10 to –30 ml/min/1.73 m²). Cockcroft–Gault classified 49% of the general population above age 60 as having an estimated GFR below their age-specific 2.5th percentile for normal kidney function as compared to 13.3% with the new MDRD formula. We therefore conclude that the MDRD formula was the best formula available for estimating GFR in the general population, and that the recommendation of the Cockcroft–Gault formula in guidelines should be reconsidered.

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Conflict of interest statement. None of the authors have a conflict of interest according to the COPE guidelines.

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