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An easy to calculate equation to estimate GFR based on inulin clearance

Dimitrios Tsinalis and Gilbert T. Thiel

Clinic for Transplantation Immunology and Nephrology, University Hospital, CH-4031 Basel, Switzerland

Correspondence and offprint requests to: Dimitrios Tsinalis; E-mail: tsinalis@gmx.net

Abstract

Background. For the estimation of renal function on the basis of serum creatinine, either the Cockcroft–Gault (CG) equation or the MDRD formula is commonly used. Compared to MDRD (using power functions), CG has the advantage of easy calculability at the bedside. MDRD, however, approaches glomerular filtration rate (GFR) more precisely than CG and gives values corrected for a body surface area (BSA) of 1.73 m^2. We wondered whether CG could be adapted to estimate GFR rather than creatinine clearance without losing the advantage of easy calculability. In this prospective study, inulin clearance under well-defined conditions was taken as the gold standard for GFR.

Methods. In 182 living kidney donors, inulin clearance was measured under standardized conditions (protein, salt and water intake, overnight stay) before and after nephrectomy. Together with the serum creatinine level, and demographic and clinical data, 281 measurements of inulin clearance were used to compare the accuracy of different estimation equations. Using stepwise multiple regression, a new set of constants was defined for a CG-like equation in order to estimate GFR.

Results. The MDRD equation underestimated GFR by 9%, and the quadratic equation suggested by Rule overestimated GFR by 12.4%. The new CG-like equation, even when calculated with 'mental arithmetic-friendly' rounded parameters, showed significantly less bias (1.2%). The adapted equation is

$$\text{GFR[mL/min]} = ((155 - \text{Age[years]}) \times \text{weight [kg]}/ \text{serum creatinine [}\mu\text{mol/L]}) \times 0.85 \text{ if female}$$

Conclusions. We propose the CG-like equation called IB-eGFR (Inulinclearance Based eGFR) to estimate GFR more reliably than MDRD, Rule's equation or the original Cockcroft–Gault equation. As our data represent a Caucasian population, the adapted equation is still to be validated for patients of other ethnicity.

Keywords: GFR estimation; GFR measurement; kidney function

Introduction

For assessment of renal function, estimation of GFR plays an important role: it is long proven to be less prone to errors than using 24 h urine collections for creatinine clearance [1] and is recommended by guideline-issuing organizations like the National Kidney Foundation [2]. As there are still conflicting data about alternative endogenous markers of kidney function like cystatin C [3], it is recommended to estimate GFR with prediction equations based on serum creatinine determinations, like the Cockcroft–Gault [4] or the abbreviated MDRD equation [5]. While the Cockcroft–Gault equation originally was designed to estimate creatinine clearance and later on shown to provide an acceptable estimation of GFR as well [6], the MDRD equation was originally designed to estimate GFR. Since this equation was published in 1999, many publications have compared the performance of the MDRD and the Cockcroft–Gault [4] equations in various populations [7–14], and different modifications or other equations have been suggested [15–18]. Several studies failed to validate kidney function estimations in potential living kidney donors against measured kidney function [19–21]. However, these studies either had a very small number of patients [19], refer to another ethnicity [20] or do not consider that the Cockcroft–Gault equation estimates creatinine clearance instead of GFR [21].

The latter is common to all of these publications: comparisons to the Cockcroft–Gault equation either do not consider that it estimates creatinine clearance instead of GFR, or it receives insufficient emphasis, for example by using a fixed correction factor [5], which seems not reasonable because of the variable tubular secretion of creatinine inversely related to GFR [22,23]. Another important issue is that in none of these studies was GFR determined by using inulin clearance. Instead, these studies employed as gold standards for GFR measurement either iothalamate [7,8,10,13,15–17], iohexol [9,12], EDTA [18] or DTPA [14], or even varying methods among patients in the same study [11,19]. For all of these methods, validation data based on comparison to inulin clearance are only available for very small numbers of patients. For example, the measurement method used to derive the MDRD formula was validated in only 20 people using inulin clearance as the gold standard [24].

In these 20 participants, the proposed method of measurement not only deviated systematically from inulin clearance but also resulted in non-systematic, significant changes between different measurements in the same subject. The authors ascribed these variations to methodical problems and noted that the small numbers of participants in each group resulted in low statistical power (40%) even for detecting big differences in clearance between groups (based on age or sex) [24]. Especially for iothalamate, it has been shown that there is a relevant tubular secretion, and in experimental studies the accuracy of iothalamate clearance was comparable to creatinine clearance [25]. So, as different methods using labelled compounds as alternative filtration markers generally were validated in very small numbers of patients and showed significant deviation from inulin clearance, the decision to use these methods in clinical trials does not seem to be based on scientific advantages over inulin clearance or at least on a solid proof of parity, but rather on practical issues, because measurement of inulin clearance is cumbersome and expensive.

The systematic determination of inulin clearance in every kidney donor evaluated at the university hospital in Basel allowed us to collect a probably unique amount of data on GFR determined by inulin clearance under standardized metabolic conditions, what still must be considered the gold standard of GFR measurement.

The objective of the current study was to use inulin clearance to assess the accuracy and precision of the IDMS-traceable MDRD equation [26,27], the quadratic equation suggested by Rule for patients with an unknown status of kidney disease [15] and the original Cockcroft–Gault equation [4]. As up to now no attempts have been made to adjust the Cockcroft–Gault equation to reflect GFR instead of creatinine clearance, we tried to adjust the Cockcroft–Gault equation for estimating GFR instead of creatinine clearance and compared the results of this adapted formula to the other equations.

Methods

Study population

Two hundred and eighty-one measurements of inulin clearance were performed in 182 consecutive living kidney donors at the university hospital in Basel. Of these, in 81 donors, inulin clearance was measured before and 1 year after donation, in 83 donors at 1 year after donation and in 18 donors both 3 weeks and 1 year after donation, resulting in 281 measurements. The basic data for the measurements are given in Table 1.

Measurement protocol

All measurements were performed after an overnight hospital stay under standardized metabolic conditions regarding intake of fluid, salt and protein. Dinner contained 35.4 g of protein and 5.8 g NaCl, and a fluid intake of 1 L of water was assured. The breakfast next morning contained 4.0 g protein and 0.6 g NaCl. After height and weight of the kidney donor were measured, a continuous intravenous hydration with 200 mL/h was given to assure water diuresis during the measurement. First, an inulin (INU-TEST®, Fa. Laevosan-lnternational AG, Zürich) loading dose of 90 mg/kg body weight was administered over 15 min. After that a constant inulin infusion was given to maintain a plasma concentration of 0.3 mg/mL. Four urine collections during 40 min each were performed under supervision of a study nurse, and blood samples were collected in the middle of each collection period. Examinations were done without bladder catheterization, as this would be potentially harmful to the patient, and because the proceeding with four consecutive collections over 40 min each easily allows us to detect collection errors by comparing the creatinine and inulin excretion of the different collection periods.

Table 1. Basic data of inulin clearance measurements

Number of donors measured	182
Before and 1 year after donation	81
Before, 3 weeks and 1 year after donation	18
1 year after donation only	83
Number of measurements	281
% of measurements after nephrectomy	71.2%
Sex (male:female)	100:181
Age (years)	50 (22–73)
Weight (kg)	67.9 (45.3–110.0)
Non-Caucasian (*n*)	0
Height (cm)	166 (147–203)
BMI (kg/m^2)]	24.6 (17.5–37.6)
Inulin clearance (mL/min)	68.5 (36.9–148.0)

Continuous variables were not normally distributed and are given as median (range).

Table 2. Established equations used for comparison

Cockcroft–Gault original equation (CG):

Creatinine clearance [mL/min] = (140 − Age [years]) × weight [kg]/(72 × serum creatinine [mg/dL]) × 0.85 if female

MDRD equation for IDMS-traceable creatinine values:

$$\text{GFR in mL/min/1.73 m}^2 = 175 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times 1.212 \text{ if black} \times 0.742 \text{ if female}$$

Quadratic equation suggested by Rule for persons with unknown status of kidney disease:

(if SCr < 0.8 mg/dL, use 0.8 for SCr)

$$\text{GFR in mL/ min /1.73 m}^2 = \exp\left(1.911 + \frac{5.249}{\text{SCr}} - \frac{2.114}{\text{SCr}^2} - 0.00686 \times \text{age} - 0.205 \text{ if female}\right)$$

Laboratory tests

Inulin in serum and urine was measured using the method described by Degenaar [28]. Serum creatinine was measured using an enzymatic assay (Wako Chemicals GmbH, D-41460 Neuss, Germany) and calibrated to values traceable to isotope dilution mass spectrometry (IDMS) as recommended by the KDIGO consensus conference [29] under participation of multiple guideline development organizations (ANZSN, CARI, ERA/EDTA, EBPG, NKF, KDOQI, UK Renal Association and CSN). The details of calibration are described elsewhere [30].

Calculations

For our comparison, we used the original Cockcroft–Gault equation, the IDMS–traceable variant of the MDRD equation [26,27] and the quadratic equation suggested by Rule *et al*. for both health and chronic kidney disease [15]. The equations are shown in Table 2.

To adapt the Cockcroft–Gault equation to GFR, we decided to use IDMS-traceable creatinine values because this calibration was recently recommended by the KDIGO conference to be used as a standard [29]. However, in the development of the original Cockcroft–Gault formula and of the equation suggested by Rule, creatinine was determined by using a non-compensated Jaffe method for use with both equations. In order to avoid distortion of the results due to applying IDMS-traceable creatinine values to equations that were designed for creatinine values determined by the Jaffe method, for use with these equations we re-calibrated our creatinine values to be comparable to Roche's Jaffe method ($\text{Cr}_{\text{Jaffe}} = 0.924 \times \text{Cr}_{\text{Enz}} + 23.693$; data from WAKO, available on request). Where needed, creatinine values expressed in μmol/L were transformed to mg/dL by dividing the value by a factor of 88.4.

We used stepwise multiple regression with internal cross-validation to determine a set of constants for a Cockcroft–Gault-like equation to reflect GFR instead of creatinine clearance, using SI units (μmol/L) for serum creatinine.

In order to compare accuracy and precision of the different equations, we transformed the results of the MDRD and Rule equations to reflect GFR not corrected for BSA, using the equation of Dubois [31].

For each equation, we analysed the correlation to inulin clearance and, more importantly, the deviation of estimation results from inulin clearance, which was calculated as (estimation result − inulin clearance) and expressed as mean bias, mean absolute bias (using the absolute size of calculated bias) and percentage of inulin clearance. The bias of different equations was assessed using least squares regression analysis and Bland–Altman [32] graphical representation in modified form by plotting the bias not against the mean of two different methods, but against the gold standard [33].

All variables were tested for normal distribution (Shapiro–Wilk *W*-test). Comparison of values was done using either a *t*-test or Wilcoxon's test, depending on the distribution of values. Frequency of categorical variables was compared using a two-tailed Fisher's exact *P*. A standard statistical software package (Statistica version 7.0 [34]) was used for analysis.

Results

As compared to the original Cockcroft–Gault equation (Table 2) containing three constants, regression analysis showed no significant improvement if serum creatinine was multiplied with a dedicated constant (like 72 in the original equation). So, we fitted the adapted equation to use only two constants, for which we found values of 154.6999 (CI 151.6781–157.7218) and 0.8349 (CI 0.8034–0.8663). To ease calculation without electronic devices, we used rounded constants (155 for the first constant and 0.85 for the second one) chosen from within the confidence interval of the calculated parameters. We call the resulting equation inulin clearance-based estimated GFR or short 'IB-eGFR'.

Table 3. The GFR-adapted Cockcroft–Gault-like IB-eGFR equation

Newly fitted equation with exact constants (exact equation): GFR [mL/min] = (154.6999 − Age [years]) × weight [kg]/serum creatinine [μmol/L]] × 0.8349 if female
Newly fitted equation with rounded constants (IB-eGFR): GFR [mL/min] = (155 − Age [years]) × weight [kg]/serum creatinine [μmol/L]] × 0.85 if female

IDMS-traceable creatinine values should be used. Creatinine given in mg% can be converted to μmol/L by multiplication with 88.4.

For our comparison with other estimation equations, we included both the results calculated with this formula using the exact constants (labelled as 'exact equation') and with rounded constants (labelled as IB-eGFR). Both equations are shown in Table 3.

While the results of all estimation equation show a good correlation to inulin clearance (Figure 1), there are significant differences regarding size and direction of the estimation bias and therefore accuracy and precision of the different estimations (Table 4). Since the original Cockcroft–Gault equation was designed to estimate creatinine clearance, it is not surprising that it gave the largest positive bias with a mean deviation from inulin clearance of 9.3 mL/min. The quadratic equation suggested by Rule showed a mean bias of +8.9 mL/min and the IDMS-traceable MDRD equation of −6.1 mL/min. The results of the newly adapted equation gave a bias of mean −0.5 mL/min when using the exact constants and +0.7 mL/min using the rounded constants (IB-eGFR), which is significantly smaller than with all other equations. The bias of different equations in relation to measured GFR is shown in Figure 2. In none of the equations, a significant dependence of the bias size on the size of GFR could be demonstrated. The smaller bias of the newly adapted equation, even when the constants used were rounded to convenient

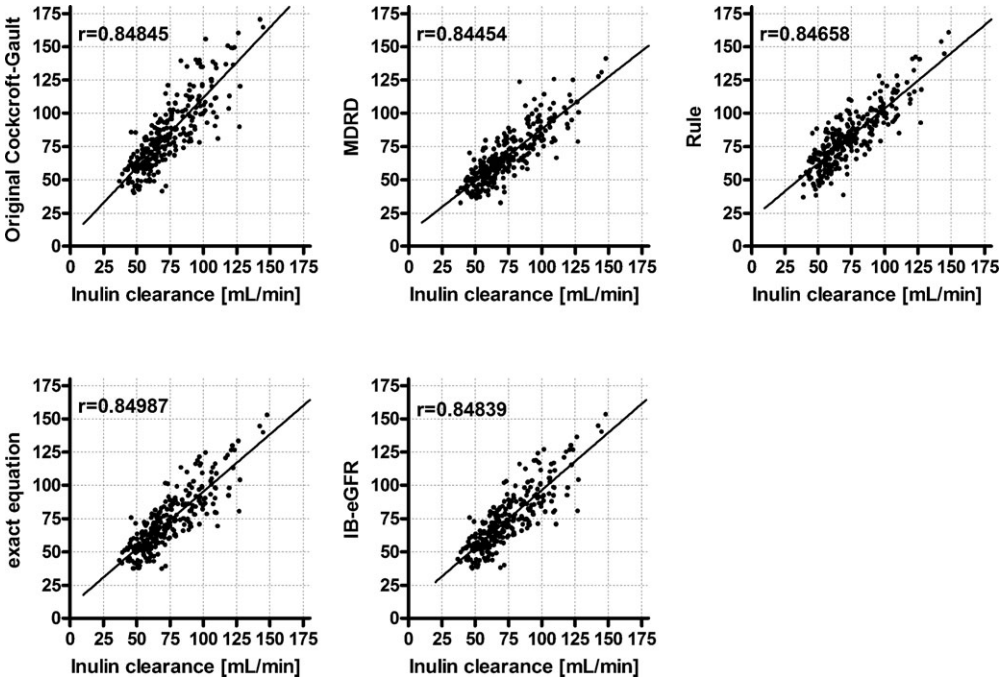

Fig. 1. Correlation of estimation results to values for inulin clearance. All estimations show a good correlation to inulin clearance without significant differences between different estimation equations.

Table 4. Comparison of different estimation equations to inulin clearance

Estimation	Correlation coefficient (r)	Mean bias (mL/min)	Mean absolute bias (mL/min)	Mean bias (% of GFR)
MDRD	0.8445	−6.1[a] (−48.2–40.6)	8.3 (0.11–48.2)	−9.0[a] (−52.2–53.6)
Rule	0.8466	8.9[a] (−34.2–39.3)	10.6 (0.02–39.3)	12.4[a] (−43.9–85.8)
CG original	0.8484	9.3[a] (−37.1–56.2)	10.8[a] (0.05–56.2)	14.3[a] (−39.8–87.6)
exact equation	0.8499	−0.5[a] (−46.5–30.3)	7.5[b] (0.05–46.5)	−0.6[a] (−45.5–65.4)
IB-eGFR	0.8484	0.7[a] (−46.3–32.7)	7.4[b] (0.04–46.3)	1.2[a] (−44.4–65.9)

Values are given as mean (range).
[a]Significant versus all other estimations.
[b]Significant versus MDRD, Rule and CG original; $P < 0.01$.

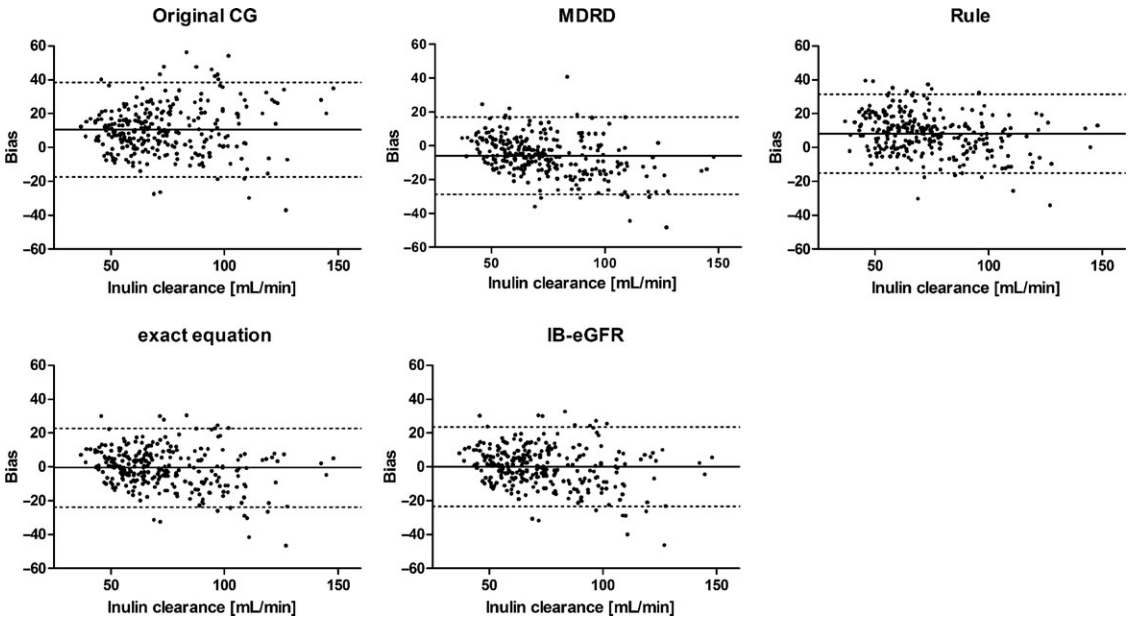

Fig. 2. Bland and Altman plot of estimation bias plotted against inulin clearance. The solid lines indicate the mean bias, and the dotted lines ± 1.96*SD of the bias.

values (IB-eGFR), gave a higher proportion of measurements below any threshold of bias selected. Figure 3 visualizes the percentage of GFR estimations with a bias of less than a given size as compared to inulin clearance under optimal conditions.

Discussion

We have tried to define an equation for estimating GFR, which is as easy to calculate as the Cockcroft–Gault formula, but aims for true GFR (as measured by inulin clearance) and is as precise as the more complicated formulae like MDRD or Rule's equation. A clinician's interest in being able to quickly estimate GFR at the bedside using a simple pocket calculator is the main reason why the Cockcroft–Gault equation became so popular everywhere. Another reason is to depend no longer on 24 h urine collections, which are often wrong (either incomplete or collected for more than 24 h or even both). The only flaw is that the Cockcroft–Gault equation is estimating creatinine clearance instead of GFR. The MDRD equation, however, has the advantage of estimating GFR, but in return carries two disadvantages. Firstly, it is no longer easy to calculate (two negative odd exponents included in the formula), and secondly, it does not give GFR as it is in absolute values (mL/min), but converted to a standardized body surface area (mL/min/1.73 m^2). Why is that a disadvantage? There are at least three reasons.

The first reason is that the BSA formula developed by Dubois and Dubois 1916 was shown to be wrong particularly in obese individuals [35;36]. We used Dubois' formula only for 'uncorrecting' GFR from BSA-adapted results (gained by MDRD or Rule's equation) back to the real values. By doing so, we were eliminating at best the bias that was introduced during the creation of both mentioned equations.

The second and most important reason is related to the main cause for using a GFR estimation equation in clinical practice. It is the adaptation of drug dosage in patients with impaired renal function. For this purpose, the effective GFR should be used and not a 'virtual' one after adaptation to BSA 1.73 m^2. This is widely accepted: the FDA is recommending GFR not corrected for BSA for conducting clinical studies in patients with impaired renal function [37]. 'Uncorrecting' MDRD for BSA for drug dosing is

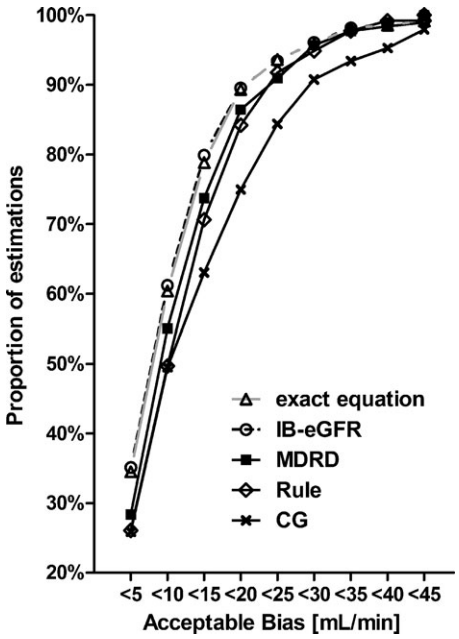

Fig. 3. Cumulative percentage of estimations below a certain bias. For example, if the acceptable bias is defined as up to 15 mL/min, the newly adapted equation will result in 79.9% of estimations meeting this criterion as compared to 73.7 and 70.6% when using the MDRD or Rule's equation, respectively, or even only 63% when using the original Cockcroft–Gault equation.

also recommended by the National Kidney Foundation [38] and the 'International Controversies Conference on Definition and Classification of Chronic Kidney Disease in Adults Worldwide' [29]. Remarkably, the latter statement was published by the initiator of the MDRD equation as first author. Conversion, however, is not easily done and certainly not at the bedside. For the conversion from mL/min/1.73 m^2 to mL/min, both weight and height are required, and the Dubois formula for BSA calculation is not easily kept in mind (BSA = Weight $^{0.425}$ × Height $^{0.725}$ × 0.007184). Using an equation for non-indexed GFR in the first place appears advantageous. We also suspect that outside the nephrology community, a large number of doctors may not realize the risk involved for over- or under-dosing drugs, when a GFR indexed for BSA 1.73 m^2 is offered.

Thirdly, in the assessment of brain-dead kidney donors, in most cases there is no time to apply more exact methods of GFR determination. From the recipient's point of view, indexing GFR to BSA is particularly misguiding in this setting. If the kidney of a dwarf donor was to be transplanted into a giant recipient, GFR correction for the donor's BSA would not help to solve the problems that would arise for the recipient.

In patients with 'normal' body size, indexing GFR to BSA has little effect on the result. However, in obese patients, indexing GFR to BSA will decrease the estimated GFR, thus concealing obesity-related hyperfiltration [39;40].

We do quite accredit the value of expressing GFR standardized to BSA when the GFR of a cohort of individuals with different weight and height has to be compared to another cohort of persons. Formulae lacking body weight may then be very comfortable to use, particularly when body weight is not available for all in the cohort. For all of the reasons mentioned above, we feel the automatic delivery of an indexed GFR result in daily clinical practice might be a risk rather than an advantage in many cases. For drug dosing in single individuals, the availability of body weight is no problem and using an indexed GFR for drug dosing—as mentioned above—is wrong. Since GFR does indeed rise with increasing body mass [40], the involvement of body weight in a GFR estimation equation adheres to the idea of using a mathematical model based on an existing causal connection, rather than relying on a pure polynomial description of a regression curve.

The worth of a GFR estimation formula depends on (1) the quality of the gold standard used for the design and validation of the equation, (2) a small deviation (bias) of the estimated GFR from GFR determined with the gold standard technique and (3) the easy calculability facilitating the use in clinical practice.

Inulin clearance measured under optimal conditions is undoubtedly the gold standard for GFR measurements. We tried to optimize the methodology by several conditions such as rest achieved by over night stay before the test, standardized protein, salt and fluid intake for 12 h before starting, standardized parenteral hydration, four phases of urine collection under constant inulin infusion, having the test performed by an experienced study nurse and many more. The only reason why inulin clearance is no longer used in most places (like in our hospital, except for experimental work in animals) is the high costs and half a day of work involved for the GFR measurement of one single patient only. It is thus no surprise that all available GFR estimation formulae are based predominantly or fully on methods replacing inulin clearance for practical reasons as mentioned in the introduction. This analysis is probably one of the very few and probably last occasions to compare results of GFR estimation formulae to a large number of inulin clearances performed under optimal conditions.

Our results confirm a good correlation of GFR results estimated by the MDRD and Rule's equation with over 280 inulin clearances (Figure 1). Also, the original Cockcroft–Gault equation is significantly correlated to Inulin clearance, despite estimating creatinine clearance. This illustrates that correlation alone is, however, not enough to assess the agreement of different methods, since a big non-random bias (constant or proportional) gives a good correlation but may render the estimation unusable. It is, thus, important to evaluate the bias of the estimation results as displayed in Figure 2 and Table 4. As expected, the original Cockcroft–Gault equation gave the largest positive bias of 14% due to the fact of being designed to estimate creatinine clearance. Creatinine secreted by tubules is added to the filtered one rendering creatinine clearance bigger than GFR. The MDRD equation tended to underestimate GFR by a mean of −9%, while Rule's equation overestimated GFR by 12% (quite close to the bias seen with the Cockcroft–Gault original formula). Using the proposed IB-eGFR equation, the mean estimation bias was significantly smaller in the range of 1%.

With any of the equations studied, big errors occurred in single patients. In fact, this is one of the flaws immanent

to all estimation equations. In the case of GFR estimation based on creatinine values, the cause of single large errors is most probably related to the creatinine value, either due to a technical error or, more likely, due to an incidental atypical creatinine peak or nadir, which has even more impact on the result the higher the GFR is. Nonetheless, with the proposed IB-eGFR equation, single large errors do not occur more frequently than with other equations, and the proposed equation is giving a higher percentage of estimations below any desired threshold, as shown in Figure 3.

The new IB-eGFR equation is made for the use with IDMS traceable creatinine values expressed in μmol/L. Similar as for the MDRD equation, only creatinine values should be used that have been recalibrated to be traceable to IDMS. The laboratory should be able to tell if this calibration is already done in the results given, or, if not, how the values have to be transformed (about +6 μmol/L for enzymatic or 'compensated Jaffe' assays, about −20 μmol/L for original Jaffe assays).

There are several limitations in this study. Firstly and most importantly, all measurements were performed in kidney donors and thus represent a healthy population. Due to the limited number of inulin clearances available, we decided to use internal cross validation for the fitting of a new equation. Further evaluation of the equation in an external cohort is desirable. Also, it would be interesting to have the IB-eGFR equation verified in other populations with different renal pathologies and a different range of GFR. In our study population, there were only few individuals with a GFR of <40 mL/min ($n = 3$) or >110 mL/min ($n = 15$), so that estimations outside this range could not be validated. Secondly, because all participants were Caucasian, a race component could not be assessed. Thirdly, several patients were measured more than once. From 182 patients, 81 donors were measured twice and 18 donors thrice (Table 1). We do not, however, consider this to be a real drawback since repeated measurements were only performed in individual subjects after substantial changes in circumstances (nephrectomy between the measurements or functional glomerular adaptation to renal loss occurring during 1 year). As individuals compensate for the loss of a kidney to a very different extent over time, we do not think that the repeated measurements introduced any false precision.

In summary, we have shown for a middle European population that both MDRD and Rule's equation do estimate GFR more exactly than the original Cockcroft–Gault equation does. However, with the application of the proposed Cockcroft–Gault-like IB-eGFR equation, GFR can be estimated with a significantly smaller bias as compared to values derived using the more complicated equations. Although the further reduction of bias may be of questionable clinical relevance and the proposed equation is still to be validated in an external cohort, the equation is helpful in situations where GFR has to be calculated at the bedside and particularly when GFR is required not to be adjusted to BSA like for individual drug dosing, the most frequent reason to use GFR estimation.

Conflict of interest statement. None declared.

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Genetic variation in the transforming growth factor-β1 gene is associated with susceptibility to IgA nephropathy

Mai Tuyet Vuong[1,2,3], Sigrid Lundberg[4], Iva Gunnarsson[1], Lars Wramner[5], Maria Seddighzadeh[1], Mirjana Hahn-Zoric[6], Anders Fernström[7], Lars Å Hanson[6], Lieu Thi Do[3], Stefan H. Jacobson[2] and Leonid Padyukov[1]

[1]Department of Medicine, Rheumatology Unit, [2]Department of Nephrology, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden, [3]Department of Internal Medicine, Hanoi Medical University, Hanoi, Vietnam, [4]Department of Medicine, Nephrology Unit, Karolinska University Hospital, Stockholm, [5]Transplantation Center, Sahlgrenska University Hospital, [6]Department of Clinical Immunology, Sahlgrenska University Hospital and Academy, Göteborg and [7]Department of Nephrology, Linköping University Hospital, Linköping, Sweden

Correspondence and offprint requests to: Leonid Padyukov; E-mail: leonid.padyukov@ki.se

Abstract

Background. There is growing evidence of genetic risk for susceptibility to IgA nephropathy. Among several candidate genes related to immunological regulation in renal tissue, *TGFB1* is known to be a contributor to proliferation and the development of fibrosis.

Methods. We analysed several SNPs in a region of this gene using 212 DNA samples from biopsy-proven IgA nephropathy patients, 146 men and 66 women and 477 healthy age-matched controls (321 men and 156 women) from the same population in Sweden.

Results. Frequencies of four out of five selected SNPs (rs6957, rs2241715, rs1800471, rs1982073 and rs1800469) were found to significantly differ between male patients and male controls in a co-dominant model (corrected $P \leq 0.05$) and of two SNPs (rs1982073 and rs1800469) in the allelic