Glomerular Filtration Rate Estimation in Prospective Living Kidney Donors: Preliminary Study

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ABSTRACT

Introduction. Kidney transplantation prolongs life expectancy in end-stage renal disease patients at a lesser cost than dialysis. Estimation of kidney function is crucial in the evaluation of prospective living kidney donors. Although unsurpassed in their precision methods of glomerular filtration rate (GFR) measurement with exogenous substances are invasive, expensive, and carry a risk for anaphylactic reactions. Alternatively, kidney function can also be assessed by GFR estimation formulas based on serum creatinine or novel markers such as cystatin C or β-trace protein (BTP). The aim of this study was to compare the performance of GFR estimation methods with reference scintigraphy-measured GFR in population of living kidney donor candidates.

Methods. We included 25 prospective kidney donors (aged 28–64 years) and measured GFR with the following equations: Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD), Mayo Clinic, Nankivell, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI; including cystatin C), and BTP based. GFR were assessed by ^{99}mTc-DTPA for reference. All estimation methods were compared with a reference by general linear models.

Results. The precision of GFR estimation by all methods is unsatisfactory (30% margin of reference held in <50% of cases). Direction of regression coefficients is negative for some of the methods even when adjusted for body mass index (BMI). Of the study subjects, 64% were overweight/obese. BMI value is significantly correlated with measured GFR ($P < .01$). CKD-EPI estimation equations are the most precise methods of GFR estimation in this analysis; in addition, CKD-EPI cystatin C and combined creatinine/cystatin C estimators are robust to overweight/obesity.

Conclusions. The precision of GFR estimation is unsatisfactory, in part because of overweight, which adversely influences measured GFR, but also renders estimation methods unusable, except for CKD-EPI cystatin C and combined creatinine/cystatin C formulae. GFR measurement with exogenous substances remains the method of choice in the assessment of kidney function in prospective kidney donors. In addition, it provides useful information on differential (split) renal function.

KIDNEY TRANSPLANTATION, a preferred method for renal replacement therapy, prolongs life expectancy in end-stage renal disease patients at a lesser cost than dialysis. Estimation of kidney function is crucial in the process of evaluation of prospective living kidney donor because of the long-term hazards of living with 1 kidney. Assessment of glomerular filtration rate (GFR) is widely used as the best estimator of overall kidney function [1]. Direct measurement of inulin clearance is the optimal method for measuring GFR

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0041-1345/14
http://dx.doi.org/10.1016/j.transproceed.2014.09.055

and is considered the gold standard of kidney function assessment. Measurement of GFR with the use of radioisotopes (ie, ^{51}Cr-EDTA, ^{99}mTc-DTPA, iothalamate with radioiodine ^{131}J or ^{125}J) or some nonisotopic substances (ie, iohexol) are also used. This procedure, however, is invasive, expensive, burdensome, and impractical or plainly unavailable in many settings. Additionally, anaphylactic reactions may occur when using any of the radioisotopic substances [2]. The reproducibility of most radioisotopic methods is questionable.

Kidney function is most commonly assessed by measurement of serum creatinine concentration or an estimation of GFR by empirical formulas usually based on serum creatinine. Both methods are inexpensive and relatively reproducible, but have numerous limitations. The association of creatinine concentration with nephrons filtration capacity is prone to the bias of many variables, including age (synthesis decreases with advancing age), gender (women synthesize less creatinine), ethnicity (Caucasians synthesize more) and body and muscle mass [3]. Moreover, creatinine concentration is inertial in its relation to GFR; it can stay in the normal range even with a $\leq$50% reduction of the initial normal GFR value [4]. This is of particular importance in the process of evaluation of kidney function in prospective kidney donors. The mean difference between estimated and measures GFR (equation bias) and accuracy of estimate (percent of estimates within 30% of the measured GFR) vary greatly between reports. Equation performance also varies markedly with overall level of kidney function [5–7]. The MDRD equation tends to underestimate GFR in patients with relatively well-preserved kidney function [5,7,8]. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation incorporates adjustment for low creatinine values and yields results that are much less underestimated compared with the MDRD equation in a nontransplant population with a high GFR [9]. However, the precision and accuracy of the equation is suboptimal, which limits its applicability in the evaluation of kidney function in prospective donors [10]. Novel filtration markers such as cystatin C and β-trace protein (BTP) are expected to be sensitive and accurate predictors of actual GFR. They were shown to predict long-term mortality of general population more precisely than creatinine-based estimators [11]. Although cystatin C is less sensitive to interindividual differences in muscle mass, this marker is increased in persons with diabetes, inflammation, and greater body mass index (BMI) [3]. BTP, also known as lipocalin prostaglandin D2 synthase, is a low-molecular-weight factor that is a member of the lipocalin protein family [12–14]. Serum BTP levels were strongly correlated with GFR in small studies of kidney transplant patients and patients with chronic kidney disease, although data are limited in other populations [15,16]. Limited data are available on the association of BTP levels with long-term outcomes. However, some reports indicate the estimation of GFR with BTP should be limited to populations with marked decrease in kidney function, the marker virtually loses its performance at a GFR of >80 mL/min [17]. Cystatin C and BTP are believed to better identify small deterioration of renal function compared with serum creatinine concentration [12,18–20].

The aim of this study was to analyze and compare accuracy and performance of different methods of GFR estimation with GFR measured by scintigraphic analysis in a population of living kidney donor candidates.

MATERIALS AND METHODS

We included 25 prospective kidney donors (aged 28–64 year; median, 48; 16 female, 9 male) in a preliminary study and tested for serum creatinine using a modified Jaffe method) [21], cystatin C (Cystatin C was determined by using a particle-enhanced turbidimetric [PET] assay [DAKO Cystatin C PET Kit] using a Cobas MIRA Plus [Hoffmann La Roche]. Reference values for the serum levels of cystatin C were: age [year], 1-50 and > 50 cystatin C [mg/L]; 0.63–1.33, and 0.74–1.55, respectively), and β-trace protein concentration. The combined (both kidneys) GFR and separate left and right GFR were then assessed by ^{99}mTc-DTPA for reference. The equations used for particular formulas were as follows:

- BTP White formula GFR (mL/min/1.73 m^2) = 112.108 × (BTP [mg/L])$^{-0.662}$ × (urea [mmol/L])$^{-0.280}$ × (0.88, if woman) [22];
- EPI creatinine: eGFR (mL/min): 141 × min(Scr/k, 1)^a × max(Scr/k, 1)$^{-1.209}$ × 0.993 age (×1.018 if female) (×1.159 if black), where Scr is serum creatinine, k is 0.7 for females and 0.9 for males, and a is −0.329 for females and −0.411 for males, min is the minimum of Scr/κ or 1, and max is the maximum of Scr/κ or 1;
- EPI cystatin C: eGFR (mL/min) = 133 × min (Scys/0.8,1)$^{-0.499}$ × max (Scys/0.8,1)$^{-1.328}$ × 0.996$^{(Age)}$ [× 0.932 if female], where min indicates the minimum of Scys/0.8 or 1 and max indicates the maximum of Scys/0.8 or 1;
- EPI combined cystatin C/creatinine: eGFR [mL/min] = 135 × min(Scr/k, 1)^a × max(Scr/k, 1)$^{-0.601}$ × min(Scys/0.8, 1)$^{-0.375}$ × max(Scys/0.8, 1)$^{-0.711}$ × 0.995$^{(Age)}$ [×0.969 if female] [×1.08 if black]) [9];
- Cockcroft–Gault: GFR (mL/min) = (140 − age [years]) × weight [kg] × (0.85 if female)/72 × serum creatinine [mg/dL] [23];
- MDRD short: eGFR (mL/min) = 186 × (0.742 if female) × (1.212 if Black) × (creatinine)$^{-1.153}$ × (age)$^{-0.203}$);
- MDRD extended: GFR (mL/min) = 198 × (serum creatinine [mg/dL])$^{-0.858}$ × (age)$^{-0.1678}$ × (0.822 if female) × (1.178 if black) × (serum urea nitrogen concentration [mg/dL])$^{-0.293}$ × (urine urea nitrogen excretion [g/d])$^{0.249}$) [24];
- Mayo quadratic formula: GFR (mL/min) = exp(1.911 + 5.249/SCr [mg/dL] − 2.114/SCr^2 − 0.00686 × age − 0.205 if female) [25]; and
- Nankivell combined creatinine/urea concentrations formula: GFR (mL/min) = 6.7/serum creatinine + 0.25 × weight − 0.5 × urea − 0.01 height^2 + 35 (25 for woman) [26].

Analysis of variance and general linear models were used for comparison of all estimation methods with a ^{99}mTc-DTPA-measured GFR. The accuracy of estimation (percent of estimates within 30% range of reference GFR) and the equation bias (mean difference between measured and estimated GFR) were calculated. $P < .05$ was considered significant.

RESULTS

The study population was aged from 28 to 64 years (median, 48), and the female to male ratio was 16/9. The mean BMI

was 26.4 ± 9.33 kg/m^2 (range, 21.5–31.2). Results of the linear regression paired comparisons are displayed in Table 1. The majority of the study population individuals were overweight or obese (normal/elevated BMI ratio was 9/16). The values of corrected GFR measured by ^{99}Tc-*DTPA* scintigraphic analysis were highly dependent on BMI (regression coefficient, −0.64; $P < .001$). Table 2 shows the results of the regression adjusted for BMI.

The data also show the relationship between BMI and measured GFR (parameter estimate for 1 unit of BMI [kg/m^2] = −6.05, which means, that with a 1 kg/m^2 increase of BMI, one could expect the measured GFR value to be reduced by 6.05 mL/min/std body surface area). The relationship of estimated and measured GFR depends greatly on body mass. The results of analysis of relation between estimated and measured GFR, according to normal and elevated BMI are presented in Table 3. The equation bias (mean difference between measured and estimated GFR) and accuracy of estimates (% of estimates within 30% of the measured GFR) are shown in Table 4.

Table 2. Estimated and Measured Glomerular Filtration (GFR) Adjusted for Body Mass Index

Parameter	^{99}Tc-*DTPA* (Corrected for Body Surface Area)		
	Parameter Estimate for Increase of 1 Unit of BMI (*P* Value)	R^2	*P* Value for the Effect of GFR Estimation Method
CKD-EPI creatine	−5.65 ($P < .01$)	0.45	NS
CKD-EPI cystatin C	−5.55 ($P < .01$)	0.44	NS
CKD-EPI cystatin C/creatine	−5.95 ($P < .01$)	0.42	NS
Cockcroft-Gault	−5.71 ($P < .01$)	0.41	NS
MDRD (short)	−6.08 ($P < .01$)	0.41	NS
MDRD (full)	−6.1 ($P < .01$)	0.41	NS
Mayo quadratic	−4.72 ($P < .01$)	0.48	0.1
Nankivell	−6.07 ($P < .01$)	0.41	NS
BTP White	−5.88 ($P < .01$)	0.43	NS
Serum creatine	−5.08 ($P < .01$)	0.45	NS
Serum cystatin C	−5.96 ($P < .01$)	0.41	NS
Serum BTP	−6.03 ($P < .01$)	0.41	NS

Abbreviations: BTP, β-trace protein; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; NS, not significant.

DISCUSSION

Estimation of kidney function is the key component of the evaluation of prospective living kidney donor. An accurate quantification of kidney filtration capacity can be obtained by calculation of clearance of exogenous substances that are not reabsorbed or secreted by renal tubules, namely, inulin. Alternatively it is possible to precisely measure the clearance of the radioactive substances, that is, Cr-EDTA, ^{99}mTc-DTPA, or iothamalate (with ^{131}J or ^{125}J isotope). Measurement of iohexal clearance, which is almost as precise as in case of radioisotopes, requires an injection of the marker and 4-point blood drawing over a period of 5 hours.

Although unsurpassed in their precision, these methods are invasive, expensive, burdensome, and carry a risk for anaphylactic reactions. A fast, readily available, and reliable estimation of kidney function is very useful when it comes to a decision if a particular person could even be possibly considered as a kidney donor. A perfect marker is expected to reflect actual kidney function, and be robust for significant deviations from the mean values of the variables used for its calculation. The endogenous markers come handy in this setting because of their simplicity, low cost, and widespread availability.

Serum creatinine–based estimators, both crude concentration and its derivatives (creatinine clearance and empirical formulas), are most commonly used. The most common and inexpensive marker used for the estimation of kidney filtration function is the serum concentration of creatinine. The creatinine is synthesized in muscles from high-energy phosphocreatine, is proportional to the muscle mass, and depends on diet. The association of creatinine concentration with nephron filtration capacity is prone to the bias of many variables. In clinical practice, the serum creatinine concentration is an approximate value.

GFR is a more precise estimator. It can be calculated from renal and serum clearance of endogenous creatinine using timed urine collection or it can be estimated by many empirical formulas. The appropriate formula depends on the population for which one seeks to estimate GFR. For example, the Cockcroft-Gault equation allows for easy and fast estimation of clearance of endogenous creatinine [23,27]. The American National Kidney Foundation recommends an equation called the MDRD, which produces values that are normalized to a standard body surface (mL/min/1.73 m^2). The MDRD formula was proposed by Hunsicker et al in 1997 [24]. The MDRD estimates lower GFR values more reliably than Cockroft-Gault equation. On the other hand, it underestimates GFR values in their normal

Table 1. Raw Relationship Between Estimated Glomerular Filtration Rate (GFR) and GFR Measured by ^{99}Tc-*DTPA* Scintigraphic Analysis

Parameter	^{99}Tc-*DTPA* (Corrected for Bod Surface Area)		
	Regression Coefficient	R^2	*P*
CKD-EPI creatine	0.33	0.12	NS
CKD-EPI cystatin C	0.29	0.09	NS
CKD-EPI cystatin C/creatine	0.16	0.03	NS
Cockcroft-Gault	−0.44	0.2	<.02
MDRD (short)	−0.01	<0.01	NS
MDRD (full)	−0.01	<0.01	NS
Mayo quadratic	−0.54	0.29	<.01
Nankivell	−0.01	<0.01	NS
BTP White	−0.23	0.05	NS
Serum creatine	−0.47	0.22	<.02
Serum cystatin C	−0.17	0.02	NS
Serum BTP	−0.09	<0.01	NS

Abbreviations: BTP, β-trace protein; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; NS, not significant.

Table 3. Subgroup Analysis of Relationship Between Estimated and Measured Glomerular Filtration Rate (GFR) According to Normal Versus Elevated Body Mass Index (BMI)

	^{99}Tc-*DTPA* (Corrected for Body Surface Area)					
	Normal BMI			Elevated BMI		
Parameter	Regression Coefficient	R^2	*P*	Regression Coefficient	R^2	*P*
CKD-EPI creatine	0.55	0.30	.12	−0.01	<0.01	NS
CKD-EPI cystatin C	0.30	0.09	NS	0.28	0.08	NS
CKD-EPI cystatin C/creatine	0.47	0.20	NS	0.21	0.04	NS
Cockcroft- Gault	−0.07	<0.01	NS	−0.38	0.15	NS
MDRD (short)	0.37	0.13	NS	−0.27	0.07	NS
MDRD (full)	0.06	<0.01	NS	−0.17	0.03	NS
Mayo quadratic	−0.32	0.1	NS	−0.49	0.24	.06
Nankivell	−0.07	<0.01	NS	−0.11	0.01	NS
BTP White	0.34	0.11	NS	−0.48	0.23	.06
Serum creatine	−0.55	0.30	.13	−0.18	0.03	NS
Serum cystatin C	−0.35	0.12	NS	−0.59	0.34	<.02
Serum BTP	0.45	0.2	NS	−0.43	0.19	.09

Abbreviations: BTP, β-trace protein; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; NS, not significant.

range. It is also less efficient in elderly and at marginal BMIs (<21 or >30 kg/m^2). The quadratic GFR equation developed by the Mayo Clinic is useful in estimations of GFR in diabetics, but it tends to overestimate GFR values in their average range.

Nankivell's equation has been developed in a kidney transplant population, and it is meant to adjust for creatinine secretion in tubules, which rises with decreasing GFR; it also incorporates the serum urea concentration. Creatinine clearance estimation, however, is heavily compliance dependent and is biased by analytic imprecision and variable rates of creatinine synthesis and elimination [10]. Muscle mass, physical activity, nutritional status, and ongoing inflammation all interfere with serum creatinine concentration, limiting its use as a robust marker of kidney function. Additionally, serum creatinine does not rise until ≤50% reduction of initial normal GFR [4,28]. Furthermore, rapid changes in GFR are not immediately detected [4]. On the other hand, there are reports showing a clear negative correlation of GFR and serum creatinine, even within normal GFR range (>90 mL/min^{-1}/[1.73 m^2]$^{-1}$) [29].

Novel markers have been proposed for GFR estimation, such as cystatin C and BTP. They are much more responsive in compromised renal function [29]. However, unlike creatinine the assays for BTP and cystatin C are commonly unavailable, costly, and most clinicians are not familiar with interpretation of their results. It has been shown that the selection of population used for construction of GFR prediction equations introduces substantial bias into obtained prediction equations [5]. The MDRD equation, for example, was derived from a cohort of chronic kidney disease patients that did not include healthy persons, and its diagnostic performance is impaired in healthy population [5]. Furthermore, most studies report correlation coefficients for the estimation methods that are insufficient to assess GFR with sufficient precision.

Because serum creatinine and creatinine clearance allow only an approximate estimation of renal function, most transplant centers performs radioisotope analysis of kidney function in prospective kidney donors. This analysis provides useful information on how filtration capacity is split between both kidneys, which in turn determines which kidney is to be harvested.

Alternatively, newer low-molecular-weight markers—cystatin C and B-trace protein—are used to assess kidney function. Cystatin C is an endogenous low-molecular-weight protein initially found in normal cerebrospinal fluid and proposed as a marker of renal function in 1985. In the kidney, it is freely filtered at the glomerulus because of its small size and lack of protein binding. It is almost completely reabsorbed in the proximal tubule and is not secreted. The normal range is slightly higher in persons >50 years old. There are no gender-related differences.

BTP, a low-molecular-weight glycoprotein (25.2 kDa) also known as prostaglandin D2 synthase, has emerged as another promising and novel marker of GFR. It is filtered through the glomerular basement membrane with minimal nonrenal elimination. BTP was also found to be increased in the serum of patients with renal failure (it was first noted in 1997). Studies have confirmed a good correlation between serum BTP levels and the GFR measurement based on inulin clearance and radioisotope methods.

The precision of GFR estimation by any of the methods analyzed in the study is disappointing, with results holding the 30% margin of reference method in <50% of cases, independent of the method. The bias (mean difference between measured and estimated GFR) may seem to be promising for CKD-EPI creatinine, both MDRD methods and Mayo quadratic method, but unfortunately the variation measures are substantial.

In addition, the direction of regression coefficients is negative for some methods. They remain negative for the Cockroft-Gault, Mayo and Nankivell equations, even after adjustment for elevated BMI. In this setting, application of

Table 4. Equation Bias (Mean Difference Between Measured and Estimated Glomerular Filtration Rate [GFR]) and Accuracy of GFR Estimates (% of Estimates Within 30% of the Measured GFR)

Parameter	Bias (mL/min; Mean ± SD)	Accuracy (%)
CKD-EPI creatine	1.2 (29.1)	28
CKD-EPI cystatin C	26.8 (36.7)	32
CKD-EPI cystatin C/creatine	17.6 (31.1)	44
Cockcroft-Gault	16.1 (46.3)	44
MDRD (short)	−0.6 (34.1)	44
MDRD (full)	4.7 (34)	48
Mayo quadratic	5.6 (41.1)	32
Nankivell	11.6 (33.4)	36
BTP White	−44 (37.2)	4

Abbreviations: BTP, β-trace protein; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease.

these methods for the purpose of kidney function estimation in apparently healthy population is questionable.

The National Kidney Foundation recommends CKD-EPI estimation equations, which proved to be the most precise methods of GFR estimation in this analysis. Furthermore CKD-EPI cystatin C combined creatinine/cystatin C equations have proved to be quite robust in overweight/obesity. Unfortunately very small sample size in this preliminary study has essentially limited the possible statistical significance of the comparisons.

The prevalence of overweight and obesity in the study population is unexpectedly high (64%). It is intriguing, especially in the group of persons considering themselves healthy enough to donate a kidney. BMI significantly correlates with measured GFR: An increase in BMI of 1 kg/m^2 is results in reduction of expected measured GFR value by 6.05 mL/min/std body surface area. Overweight not only negatively influences the measured GFR value, but also renders most of the estimation methods unusable, with the exception of CKD-EPI cystatin C and, to a lesser extent, combined creatinine/cystatin C formulas. Generally, patients with concomitant diseases or chronically taking medications are known to have less reliable GFR measured by DTPA (probably because of alterations in protein-binding of DTPA) [30]. We are also not sure if and how an increased ratio of fat tissue may influence reliability and reproducibility of the DTPA scintigraphic measurement of GFR [31].

Another possible explanation of a poor precision of GFR estimation method in our study is the well-known low performance of kidney function markers, namely, creatinine, cystatin C, and BTP, in persons with normal or minimal decline of renal function. The correlation of these markers with a reference GFR at higher values of GFR is rather vague and it may easily confound the results. Because of the preliminary nature of the study with a very limited number cases to investigate ($n = 25$), results should be interpreted with extreme caution.

Exogenous substance clearance measurement remains the most reliable method of kidney function estimation, because the performance of less invasive methods of estimation is not satisfactory, in particular in overweighed persons. In addition, scintigraphic DTPA GFR measurement provides very useful information on differential (split) renal function.

In conclusion, the precision of GFR estimation is unsatisfactory, in part because of overweight, which adversely influences measured GFR, but also renders estimation methods unusable, except for CKD-EPI cystatin C and combined creatinine/cystatin C formulas. GFR measurement with exogenous substances remains the method of choice in assessment of kidney function in prospective kidney donors. In addition, it provides useful information on differential (split) renal function.

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