Chapter seven

Use of estimated GFR in donor screening would needlessly reduce the living kidney donor pool.
Renal awareness: use of MDRD in donor screening would needlessly reduce the living kidney donor pool: a Bayesian approach

Submitted

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Abstract

Estimated GFR (eGFR) by MDRD is automatically provided with serum creatinine measurement in many laboratories. MDRD gives a cheap and easy estimate of GFR but performs poorly in subjects without renal impairment. Prospective living kidney donors should have a glomerular filtration rate above 80 ml/min/1.73 m² to donate. Considering the underestimation of GFR by eGFR, donors in whom eGFR is ≤80 ml/min/1.73 m² may be refused whilst their true GFR is above the threshold.

We therefore analysed eGFR in comparison to GFR (¹²⁵I-iothalamate) in 249 consecutive living kidney donors (50±11 years, 56% female) before nephrectomy and analysed post-donation GFR in donors with eGFR below 80. Finally, we applied a Bayesian approach in 335 subsequent subjects screened for kidney donation to calculate the probability of true GFR below the threshold of 80 ml/min/1.73 m² given an eGFR below 80.

210 out of 249 donors (62% female) had pre-donation eGFR <80; their true GFR was 102±15 ml/min/1.73 m². Their post-donation GFR was 65±10 ml/min/1.73 m² in donors with pre-donation MDRD>80 (p=0.002). Donors with eGFR<80 were more often female and significantly older. Applying Bayes’ theorem on the screened population of 335 subjects (mean GFR 103±16 and eGFR 71±10 ml/min/1.73 m²), the probability that a person with eGFR<80 would indeed have a true GFR<80 ml/min/1.73 m² was 7.5%.

Thus, donors who would not have been eligible to donate based on eGFR<80, displayed adequate and acceptable renal function after donation. Use of eGFR for selection of kidney donors leads to an unnecessary reduction of the donor pool.
Introduction

In the Netherlands and many other countries worldwide, it is currently common practice for laboratories to report an estimated glomerular filtration rate (eGFR) as derived from the Modification of Diet in Renal Disease study equation (MDRD) when a blood sample is sent in for creatinine measurement. The eGFR is advocated for cheap and simple estimation of renal function. However, it was developed in a population with renal disease and performs poorly in subjects without renal function impairment. It is well-known that the eGFR considerably underestimates true GFR in the normal and higher ranges of renal function [1-3]. Yet, its use is widespread, due to lack of simple alternatives.

Prospective living kidney donors have to meet strict criteria to be eligible to donate. Most centres employ a threshold for GFR or creatinine clearance at 80 ml/min/1.73 m² [4]. Considering the underestimation of true GFR by eGFR, this could imply that subjects in whom eGFR is below 80 ml/min/1.73 m² are discouraged to enter screening or are refused for donation while their true GFR is actually above the threshold. This could lead to unnecessary reduction of the donor pool. In our centre, renal function measurement during screening and follow-up of living kidney donors is performed by iothalamate clearance, i.e. the gold standard for renal function assessment. We hypothesized that in a substantial proportion of our actual donor population, eGFR would have been below the 80 ml/min/1.73 m² threshold before donation. This may thus have led to declining these individuals as donors, had no other assessment of renal function been available.

To analyse for the impact of the use of eGFR in this specific healthy population, we compared eGFR to true GFR in 249 consecutive living kidney donors. First, we established what proportion of the population would have been declined for donation had eGFR been used instead of iothalamate clearance and whether this population has specific characteristics. Second, we analysed early post-donation outcome for these donors with eGFR below 80 ml/min/1.73 m², as compared to donors with eGFR above 80 ml/min/1.73 m².

Finally, we applied the Bayesian approach to predict the probability of true GFR below 80 ml/min/1.73 m² in a population of subjects screened for donation. For this purpose, we analysed a total of 335 subsequent subjects who were screened for donation, including both the abovementioned accepted donors and subjects who were declined for donation, as will be described below. In all subjects, true GFR was routinely measured by 125I-iothalamate clearance and eGFR derived from a simultaneously drawn serum creatinine sample.

Subjects and methods

For the first part of our analysis, we retrospectively evaluated data from 249 consecutive living kidney donors who donated between 1996 and 2007 and who completed the routine screening and follow-up protocol. GFR was measured as the clearance of 125I-iothalamate 4 months before and 2 months after kidney donation; the eGFR was calculated from blank blood samples drawn on these same days. Since eGFR by MDRD is expressed as ml/min per 1.73 m² body surface area (BSA), GFR was normalized for body surface area (GFR_{BSA}) to allow comparison with eGFR, as described below.
Creatinine measurements and calibration

In our centre, in blood samples drawn after the 1st of March 2006, serum creatinine was measured by enzymatic assay on the Roche Modular. Before this date, samples had been measured by Jaffé alkaline picrate assay. Both methods were calibrated to the reference standard, i.e. Cleveland Clinic Laboratory measurements, were the MDRD equation was developed. For this purpose, a total of 535 blood samples with a broad range of creatinine were sent to the Cleveland Laboratory, 177 of which were from before March 1 2006. Samples for calibration purposes were stored at -80°C until measured. Calibration equations were as follows: calibrated serum creatinine = \[0.8025 \times (\text{UMCG Jaffé creatinine values in } \mu\text{mol/l}) + 24.504\] for measurements before the 1st of March and \[0.9880 \times (\text{UMCG Roche creatinine values in } \mu\text{mol/l}) + 11.359\] for measurements after the 1st of March. MDRD was calculated from calibrated creatinine values.

Bayesian approach on subjects screened for donation

For the Bayesian analyses, we extended our abovementioned donor population with the other subjects who had been screened for donation from 2001 to 2006. This was done to limit the selection bias when calculating Bayes’ theorem with data from accepted donors –likely a more healthy population– while subsequently applying its implications to a broader population of potential donors.

In our centre, most potential donors enter the screening protocol after referral by the prospective recipient’s general nephrologist and thus typically come from a general hospital. A first, rough assessment has usually been performed by then, and it is uncommon for subjects in due course to be declined on grounds of inadequate GFR.

We included 300 subjects who were fit for donation, including the 249 donors from our previous analyses and 51 donors who were on the waiting list for donor nephrectomy or who did not complete the follow-up measurements yet at time of this report. An additional 35 subjects were screened but donor nephrectomy did not proceed due to various reasons, both on non-medical grounds (motivational objections or recipient unfit for transplantation, n=9) and on medical grounds (impaired glucose tolerance,

### Table 1. Donor characteristics prior to living kidney donation.

<table>
<thead>
<tr>
<th></th>
<th>Male (n=110)</th>
<th>Female (n=139)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50±12</td>
<td>49±9</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26±4</td>
<td>26±4</td>
<td>NS</td>
</tr>
<tr>
<td>Absolute GFR (ml/min)</td>
<td>123±19</td>
<td>109±18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normalized GFR (ml/min/1.73 m²)</td>
<td>103±14</td>
<td>103±16</td>
<td>NS</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>75±9</td>
<td>66±8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deviation of eGFR from normalized GFR</td>
<td>26±9%</td>
<td>35±11%</td>
<td>&lt;0.001</td>
</tr>
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</table>

eGFR was significantly lower than absolute and normalized GFR, both p≤0.001. Normalized values represent crude data corrected for body surface area. Differences between male and female donors were analysed by Student’s t-test. Abbreviations: NS, not significant; GFR, glomerular filtration rate; eGFR, estimated GFR by MDRD equation.
n=4; hypertension or cardiovascular, n=7; GFR inadequate for donation, n=3; a combination of these, n=3; and other grounds e.g. malignancy, aneurysm, retroperitoneal fibrosis, together n=9). All 335 subjects thus obtained underwent routine screening by iothalamate clearance and eGFR was calculated.

Bayes’ theorem was applied to predict the probability of a true GFR below 80 ml/min/1.73 m² given an eGFR below 80 ml/min/1.73 m² in these 335 subjects. Calculations were as follows: (posterior chance = (prior * likelihood) / evidence), i.e. \( p(A|B) = \frac{p(A) * p(B|A)}{p(B)} \). By means of this model, a priori evidence (i.e. the prevalence \( p(A) \) of true GFR below 80 in the screened population) is thus taken into account for determination of the conditional post priori chance \( p(A|B) \) of a true GFR below 80, in which the condition is the probability \( p(B) \) of an eGFR below 80 ml/min/1.73 m². For the analyses, the population was subdivided by gender, median age (50 years) and normal weight or overweight (BMI 25) and hereby subpopulations of more or less equal size were obtained.

**Calculations and statistical analyses**

Estimated GFR was calculated as follows: MDRD = 186 * (serum creatinine in mg/dl)^-1.154 * (age)^-0.203 (* 0.742 if female). BSA was calculated as 0.007184 * (height in cm)^0.725 * (body weight)^0.425. Where applicable, GFR was normalized for BSA to compare with MDRD. Normalized values were obtained by dividing renal function by BSA and multiplying by 1.73 m². Body mass index (BMI) was calculated as [body weight in kg] / [length in m]² and divided into classes: normal weight: BMI <25 kg/m², overweight: BMI 25-29.9 kg/m², obesity: BMI ≥30 kg/m².

Analyses were performed using SPSS software version 14.0 and GraphPad Prism version 4.03 for Windows. Data are given as mean ± standard deviation, unless stated otherwise. Pearson’s Correlation coefficients were calculated to account for univariate correlations. Student’s paired t-test was used to compare post-donation to pre-donation values. Analyses were performed for male and female donors separately. We divided the population of actual donors by a break-up according to the recommended lower limit for donation of 80 ml/min/1.73 m² and compared true GFR and post-donation GFR in donors with pre-donation eGFR below and above this threshold.

**Results**

For the group of 249 donors as a whole, mean age was 50±11 years, mean BMI 26±4 kg/m², and 56% were female. Before donation, uncorrected true GFR was 115±20 ml/min. After normalization for body surface area (BSA), pre-donation GFR was 103±15 ml/min/1.73m². Mean pre-donation eGFR was 70±10 ml/min/1.73 m².
Table 1 shows donor characteristics for female and male donors separately. There were no differences in age and BMI between male and female donors. In male donors, eGFR was significantly higher, this was not the case for GFR after normalization for BSA.

**Extent of underestimation by eGFR**

True GFR was underestimated by eGFR by an average of 31±11%. As anticipated, the underestimation was larger in the higher ranges, as shown by Bland-Altman plot in figure 1, R^2=0.16; p≤0.001. The underestimation of true GFR by eGFR was significantly larger in women (also table 1).

**Comparison of donors with eGFR below or above 80 ml/min/1.73 m^2**

Pre- and post-donation data are given by a break-up by pre-donation eGFR below or above 80 ml/min/1.73 m^2 in table 2. It shows that 210 out of 249 donors (of whom 62% female) had a pre-donation eGFR below the limit of 80 ml/min/1.73 m^2. This amounted to 84% of the total number of subjects accepted to donate a kidney in our centre. Donors with an eGFR below 80 were more often female and significantly older than donors with pre-donation eGFR above 80 ml/min/1.73 m^2. True renal function by normalized GFR was significantly higher in these donors, as can also be seen in table 2, which lists true and estimated GFR with a break-up at estimated GFR of 80 ml/min/1.73 m^2.

Post-donation renal function was significantly lower in donors with a pre-donation eGFR below 80 ml/min/1.73 m^2 than in those with eGFR above 80 ml/min/1.73 m^2, but the difference was relatively small, with a true GFR of 65±10 versus 70±10 ml/min/1.73 m^2 (p=0.002). The decrease in true GFR due to donor

<table>
<thead>
<tr>
<th>Pre-donation</th>
<th>≤80 (n=210)</th>
<th>&gt;80 (n=39)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (ml/min/1.73 m^2)</td>
<td>67±7</td>
<td>86±6</td>
<td>≤0.001</td>
</tr>
<tr>
<td>Female donors (number; %)</td>
<td>131 (62%)</td>
<td>8 (21%)</td>
<td>≤0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51±10</td>
<td>42±11</td>
<td>≤0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m^2)</td>
<td>26±4</td>
<td>26±4</td>
<td>NS</td>
</tr>
<tr>
<td>True GFR (ml/min/1.73 m^2)</td>
<td>102±15*</td>
<td>110±14*</td>
<td>≤0.001</td>
</tr>
</tbody>
</table>

| After donation | | | |
|----------------| | | |
| eGFR (ml/min/1.73 m^2) | 50±6 | 60±7 | ≤0.001 |
| True GFR (ml/min/1.73 m^2) | 65±10* | 70±10* | 0.002 |
| Decrease in MDRD | 25±7% | 29±8% | ≤0.001 |
| Decrease in true GFR | 36±7%* | 36±8%* | NS |

**Table 2. Pre- and post-donation characteristics for eGFR below or above 80 ml/min/1.73 m^2.**

The population was divided into two groups: donors with eGFR below or above 80 ml/min/1.73 m^2. True GFR was normalized for body surface area. Differences were analysed by Student’s t-test and chi-square. Abbreviations: NS, not significant; GFR, glomerular filtration rate; eGFR, estimated GFR (by MDRD). * p<0.001 for GFR vs. eGFR or decrease in GFR vs. decrease in eGFR (paired t-test).
nephrectomy, expressed as a percentage, was similar between both groups.

**Predicted probability of true GFR below 80: a Bayesian approach**

Finally, we calculated the probability that a potential donor who presents with eGFR below 80 ml/min/1.73 m² would indeed have a true GFR below 80 ml/min/1.73 m², taking into account the posterior probability of a GFR<80 in this particular population. For this purpose, data from 335 subjects who were screened as potential donors were analysed; 56% were female, with a mean age of 49±11 years and a mean BMI of 26±4 kg/m². Mean true GFR was 103±16 ml/min/1.73 m² and eGFR was 71±10 ml/min/1.73 m². Of these subjects, 279 had eGFR below 80. 21 subjects had in fact a true GFR below 80 ml/min/1.73 m², all of whom had an eGFR below 80. This is presented in table 3.

According to Bayes’ theorem, the probability that a potential donor who presents with eGFR below 80 would have a true GFR below 80 ml/min/1.73 m² was 7.5% for the screened population as a whole. Figure 2 shows an ROC curve for sensitivity and specificity of eGFR in predicting true GFR below 80 ml/min/1.73 m². The area under the curve was 0.73±0.05. Because eGFR is known to perform better in the lower ranges, we also applied an ROC curve for eGFR predicting true GFR below 75 ml/min/1.73 m². The area under the curve was slightly larger for this second curve (AUC 0.81±0.05), however the difference was not of statistical significance compared to the first curve.

The predicted probability was further analysed according to gender, age and BMI, as presented in figure 3, which shows a flow chart of the predicted probability of true GFR below 80 ml/min/1.73 m² when specific donor characteristics are taken into account. The population was subdivided by gender, median age and normal weight or overweight. Hereby, groups of more or less similar size were obtained. As can be derived from figure 3, the probability of a true GFR below 80 ml/min/1.73 m², given an eGFR below that threshold ranged from 0% to 19.1%, depending on gender, age and BMI.

**Discussion**

In the past years, much effort has been put in promoting the general awareness on presence of renal function impairment in subjects without known renal disease. Recent developments include the automated report of eGFR by laboratories when serum creatinine is measured. Thus, easy access to a renal function estimate was established, further contributing to renal awareness. However, there are pitfalls to the use of eGFR in subjects without renal disease. The underestimation of true
GFR by eGFR in subjects with normal or mildly impaired renal function is well-established [2,5]. Our current data are in line with this, and the underestimation of true GFR by eGFR is quantitatively comparable to prior studies. Our current study analyses possible consequences for living kidney donation. Remarkably, the vast majority of our prospective living kidney donors would not be considered eligible to donate based on their eGFR. Despite an eGFR below the threshold of 80 ml/min/1.73 m², these subjects would be eligible to donate based on their true GFR by iothalamate clearance. Out of 335 subjects, 279 presented with eGFR below 80, whereas only 21 subjects indeed had a true GFR below 80 ml/min/1.73 m². This strikingly low proportion is not only due to relatively low accuracy of eGFR as such, but also to the lower prior probability of renal function impairment in the population studied. Taking into account the prevalence of the condition that is to be detected, is the basis of Bayes’ theorem. In the general population, the prevalence of renal function impairment is low – in other words: the number of individuals in whom eGFR is anticipated to underestimate true GFR by far exceeds the number of individuals in whom eGFR performs properly. i.e. subjects with impaired renal function. Kidney donors represent a healthy selection of the general population [6]. Likely, this will also apply to some extent to subjects screened for donation. Accordingly, the probability of true renal function impairment in our study was very low, even in subjects with an eGFR below 80 ml/min/1.73 m².

Our short-term follow-up data show that when persons with eGFR below 80 and true GFR above 80 do donate, renal outcome after donor nephrectomy is good. Rule et al. previously stated that GFR cannot be estimated accurately in prospective kidney donors by eGFR due to the weak correlation with true GFR [7]. Our study not only confirms that eGFR is unsuitable for screening purposes but in addition, we are the first to show that post-donation renal function is indeed adequate in subjects who would have been discarded as donors had eGFR been used.

We calibrated our creatinine values to comply with the original MDRD laboratory, as proposed by Coresh et al. [8,9] to preclude that differences in the creatinine assay would influence the accuracy of eGFR. Recently, Wetzels et al. provided reference values for MDRD in a large Caucasian population without further identifiable risk. From their data can be derived that in a healthy population, over 50% of males above the age of 50 have

<table>
<thead>
<tr>
<th>Table 3. Characteristics of screened subjects by eGFR and true GFR at 80 ml/min/1.73 m².</th>
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<tbody>
<tr>
<td>335 subjects were screened for living kidney donation; true GFR was measured by 125I-iothalamate clearance and normalized for body surface area, eGFR was determined by MDRD. Abbreviations: eGFR, estimated GFR; GFR, glomerular filtration rate, in ml/min/1.73 m²; n/a, not applicable. * p-value by ANOVA or χ².</td>
</tr>
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<table>
<thead>
<tr>
<th>eGFR</th>
<th>True GFR&lt;80</th>
<th>eGFR&gt;80</th>
<th>True GFR&gt;80</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>eGFR&lt;80</td>
<td>eGFR&gt;80</td>
<td>eGFR&lt;80</td>
<td>eGFR&gt;80</td>
</tr>
<tr>
<td>Total number (% female)</td>
<td>21 (62%)</td>
<td>n/a</td>
<td>258 (63%)</td>
<td>56 (21%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62±9</td>
<td>n/a</td>
<td>50±10</td>
<td>43±13</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.7±2.9</td>
<td>n/a</td>
<td>26.0±4.0</td>
<td>26.1±4.2</td>
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an eGFR below 80 ml/min/1.73 m². For females, already above the age of 35, half of the population has an eGFR below 80 ml/min/1.73 m² [12]. These data suggest that, when eGFR is used, the definitions of “normal” renal function should be adjusted.

The performance of eGFR depends on age, gender and BMI [10,11]. The predicted probability of a true GFR below 80, given an eGFR below 80, can be anticipated to be modified by these characteristics, as illustrated by our analysis in figure 3.Subjects in whom eGFR performed better were more often female and older.

It is generally appreciated that renal function estimation from serum creatinine in a (presumed) healthy population will remain problematic. Equations using cystatin C, or a combination of creatinine and cystatin C have been proposed to overcome the limitations of creatinine-based formulas [13]. However, in a population of kidney donors, cystatin C seems to perform similarly to creatinine-based equations [14,15].

Our study has several limitations. It is a single centre study and our study population is of relatively normal weight. This limits generalizability to a population where overt obesity is more common in kidney donors, such as in the United States. Furthermore, our population is predominantly white. Our probability model may therefore not be generalizable

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**Figure 3. Predicted probability of true GFR <80 ml/min/1.73 m² by Bayes’ theorem.**

Probabilities are calculated by Bayes’ theorem, applied to a population of 335 subjects who were screened for kidney donation. Age 50 was chosen because it represented median age in the total group. The number of subjects in each subgroup was as follows: a n=25; b n=45; c n=26; d n=52; e n=55; f n=47; g n=36; h n=49.
to other potential donor populations. Finally, we could not provide data on how many potential donors do not make it to the screening program due to a given value of eGFR obtained in general practice.

So what would be the implications of our analyses? Fortunately, most centres use creatinine clearance or isotope clearance for renal function assessment of their potential donors [4]. However, as mentioned above, recent programs for renal awareness have promoted reporting eGFR by MDRD when creatinine is measured and many laboratories currently do so in an automated fashion. For correct reporting and interpretation of eGFR, on the one hand creatinine should be calibrated and on the other hand, one should be aware of the limitations of eGFR, in particular in a healthy population. In conclusion, inadvertent use of renal function estimates can lead to unnecessary reduction of the donor pool. In particular in older donors and females, eGFR can be below the advised threshold while true GFR is actually above it. When initial screening reveals an eGFR below 80, or when an eGFR below 80 is in the subject’s prior records, a prospective donor should not be turned down immediately nor be discouraged to enter the screening program, but a more sensitive renal function measurement is warranted [16]. In our population, the majority of prospective donors would not have been eligible to donate when merely the eGFR would have been applied. In these donors, short term residual renal function after donation was adequate. Whereas long-term data are still needed to confirm long-term safety, the short-term data suggest that donation in these subjects is safe provided that true GFR is sufficient. Certainly, not many centres solely rely on use of MDRD for screening of kidney donors, as most use 24-hour creatinine clearance [4,17]. However, we should realize that screening commences prior to referral and many potential donors may not even make it to the transplant surgeon’s or nephrologist’s doorstep.
References


