Comparison of $^{99m}$Tc-DTPA renal dynamic imaging with modified MDRD equation for glomerular filtration rate estimation in Chinese patients in different stages of chronic kidney disease

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Abstract

Background. The renal dynamic imaging method (modified Gate’s method) with $^{99m}$Tc-diethylene triamine pentaacetic acid ($^{99m}$Tc-DTPA) is simple and less time consuming for glomerular filtration rate (GFR) estimation than other methods. However, its diagnostic performance as a surrogate marker of GFR is questioned increasingly. Recently, the modified Modification of Diet in Renal Disease (MDRD) study equation based on data from Chinese patients of chronic kidney disease (CKD) showed significant performance improvement. In the present study, the renal dynamic imaging methods and the modified abbreviated MDRD equation were compared with the plasma clearance method.

Methods. Four hundred and eighty two patients with CKD were selected. GFR were estimated simultaneously using three methods: (i) modified Gate’s method (gGFR); (ii) the modified abbreviated MDRD equation (c-aGFR) and (iii) dual plasma sampling method (rGFR). Using rGFR as the reference method, gGFR and c-aGFR were compared with rGFR in each stage of CKD.

Results. Both gGFR and c-aGFR were correlated well with rGFR ($r_{gGFR} = 0.81$ and $r_{c,aGFR} = 0.90$, $P < 0.001$). In the overall performance, c-aGFR had less bias (849.5 vs 933.1 arbitrary units), higher precision (57 vs 78.4 ml/min/1.73 m$^2$) and higher accuracy than gGFR. For gGFR, the 15, 30 and 50% accuracies were 32.4, 56.0 and 79.1%, respectively; for c-aGFR, the corresponding accuracy rose to 43.2%, 75.5% and 90.9%, respectively. In each stage of CKD, the modified abbreviated MDRD equation also outperformed the modified Gate’s method in the GFR estimation.

Conclusion. Our results indicated that the performance of the renal dynamic imaging in total GFR estimation was not better than the modified abbreviated MDRD equation in our patient group, and should not be used as a surrogate marker of GFR, especially in clinical trials. We presume that the dynamic renal imaging methods for estimation of GFR can be improved by using proper reference GFR, more adequate background subtraction and soft-tissue attenuation correction, in a relatively larger sample size.

Keywords: dual plasma sample method; glomerular filtration rate; modified abbreviated MDRD equation; renal dynamic imaging; $^{99m}$Tc-DTPA

Introduction

Renal dynamic imaging with $^{99m}$Tc-diethylene triamine pentaacetic acid ($^{99m}$Tc-DTPA) is a commonly used method to determine renal blood flow and unilateral kidney function. The timed uptake curves of the two kidneys, especially the comparison, give notable information such as quantitative unilateral renal function and pathophysiological changes in the kidney in renovascular hypertension, hydronephrosis and renal transplant [1–4]. The most popular calculation method nowadays is the modified Gate’s method, which is commercially available. To measure glomerular filtration rate (GFR) using this kind of gamma camera method, no blood and urine collection is needed, and measurement takes only 20 min approximate [1]. Because of its convenience, it is usually used as a surrogate of GFR in some clinical trials [2–4].

Recently, many studies have been conducted to test the accuracy of the modified Gate’s method in estimation of GFR. John et al. [5] compared the $^{99m}$Tc-DTPA renal dynamic imaging method with $^{99m}$Tc-DTPA plasma clearance as the reference GFR (rGFR), and found significant difference between the modified Gate’s method and rGFR.
Using inulin clearance as the reference standard, Natale et al. [6] indicated that the Gate’s method tended to overestimate GFR at low levels, and underestimate GFR at high levels of GFR. A recent published study from Itoh et al. [7] also found a similar result in their study the performance of the renal dynamic imaging method was even worse than creatinine clearance in GFR estimation. Because of the limit of sample sizes, these studies could not clarify the detailed performance of the modified Gate’s method in different stages of chronic kidney disease (CKD).

Also, GFR can be calculated from creatinine-based estimating equations, which are simple, time-saving, and cost-effective. Among the creatinine-based equations, the abbreviated Modification of Diet in Renal Disease study (MDRD) equation [8] was the most popular because of its simplicity and acceptable performance [9–11]. But Asian subjects were not included in the MDRD study, and our previous work found that this equation to estimate GFR underestimated rGFR in upper-normal kidney function and overestimated GFR in advanced renal failure [12]. Thus, we modified the MDRD equations based on data from Chinese CKD patients [13], and the performance of the modified equations was much better than the original one. It is not known if the modified abbreviated MDRD equation could provide more advantages than the renal dynamic imaging method in GFR estimation.

The current study was undertaken to clarify the detailed accuracy of the modified Gate’s method in different stages of CKD. GFR estimated by the renal dynamic imaging method (gGFR) and the modified abbreviated MDRD equation (c-aGFR) were compared with 99mTc-DTPA plasma clearance (rGFR).

Subjects and methods

Patients

This was part of our study of modification of MDRD equations for Chinese CKD patients [13] and participants from the Peking University First Hospital were included in the present analysis. The inclusion and exclusion criteria are described elsewhere [13]; briefly, patients with acute kidney function deterioration, oedema, skeletal muscle atrophy, pleural effusion or ascites, malnutrition, amputation, heart failure or ketoacidosis were excluded. Patients who were taking cimetidine, trimethoprim or those who were on any renal replacement therapy were also excluded. A total of 482 patients were included.

CKD was diagnosed and staged according to the Kidney Disease Outcome Quality Initiatives (K/DOQI) clinical practice guideline [10].

Methods

Measurement of GFR using the 99mTc-DTPA renal dynamic imaging method [1]. 99mTc-DTPA renal dynamic imaging (modified Gate’s method) was measured by Millennium TM MPR SPECT from General Electric Medical System. Patients were hydrated with 300–500 ml water after breakfast, 20 min prior to examination. A 6 s count of the syringe containing 99mTc-DTPA (5 mCi, from Beijing Atom Hightech Co. Ltd., radiochemical purity 95%) was performed before injection. After a bolus of intravenous injection of 185 MBq 99mTc-DTPA into the patient’s forearm, the dynamic imaging acquisition was carried out in the posterior position. Regions of kidneys and bladder were placed in the center view of the gamma camera. The post-injection syringe was counted similar to pre-injection. The pre-count minus the post-count provided a total injected dose.

Region of interest (ROI) for each kidney was drawn manually on the frame, from 1 to 3 min following the injection. The semi-lunar regions of interest were placed around the lower, outer renal margins, as initially outlined with a light pen. The background corrected time–activity curve was generated, and the renal uptake of unilateral kidney for 1 min from 2 to 3 min after the injection was calculated.

After image acquisition, patient’s weight and height were entered into an online computer, with which all imaging data were recorded. The gGFR was automatically calculated by a commercially available computer according to the Gate’s algorithm.

GFR by modified Gate’s method [1] was calculated with the following formula:

$$\text{Total renal uptake percent (\%) = } \frac{\left[ (R - RB) e^{-\mu R} + (L - LB) e^{-\mu L} \right]}{\text{Pre} - \text{Post}} \times 100$$

where Pre: pre-count, Post: post-count, R: right kidney counts, RB: right kidney background counts, L: left kidney counts, LB: left kidney background counts, \(\mu\): attenuation coefficient of 99mTc in soft tissue (0.153/cm), e: constant.

99mTc-DTPA plasma clearance measured by dual plasma sampling method (rGFR). 99mTc-DTPA plasma clearance was measured simultaneously with renal dynamic imaging; two plasma samples method was used. After image acquisition, heparin anti-coagulated blood samples were taken 2 and 4 h after injection from the opposite forearm. In patients with a c-aGFR (estimated GFR by modified abbreviated MDRD equation) less than 30 ml/min/1.73 m², delayed plasma samples were drawn for more precise GFR measurement: the first blood sampling was obtained 3 h and the second blood sampling was obtained 5 h after injection (or even in 24 h of the second blood sampling in patients with a c-aGFR less than 15 ml/min/1.73 m²). Plasma was separated (3 ml anti-coagulated blood centrifuged for 15 min at a speed of 1500 g), and radioactivity in the plasma (1 ml) was counted in multi-function well counter (HY-901 multi-function instrument from Beijing Six in Company).
where $D$: dosage of drug injected; $T_1$: time of first blood sample (about 2 or 3h); $P_1$: plasma activity at $T_1$; $T_2$: time of second blood sample (about 4 or 5h or even 24h); $P_2$: plasma activity at $T_2$. Units for $D$, $P_1$ and $P_2$ were cpm/ml; units for $T_1$, $T_2$ was minute.

Decay of radioactive activity was corrected:

Corrected radioactivity = Measured activity $\times \exp(-\ln(2) \times \text{Interval}/6.02)$

Estimation of GFR from modified abbreviated MDRD equation [13]. The GFR (c-aGFR) was also estimated from plasma creatinine (Pcr) using modified abbreviated MDRD equation based on data from Chinese CKD patients:

$$c - a\text{GFR}(\text{ml/min}/1.73\text{ m}^2) = 175 \times \frac{\text{Pcr}^{-0.234}}{\text{age}^{-0.179}} \times (0.79\text{ if female})$$

where Pcr was in unit of mg/dl; age was in years.

Pcr levels were measured in a single laboratory (Department of Laboratory, Peking University First Hospital, normal reference range, 0.72–1.48 mg/dl or 64–131 μmol/l) on a Hitachi 7600 analyser using the Jaffe’s kinetic method with a sample blank, which is described elsewhere [12].

Statistical analysis

The estimated GFRs (eGFR, including gGFR and c-aGFR) were compared with rGFR using Bland–Altman analysis. The difference between eGFR and rGFR was defined as eGFR minus rGFR; the absolute difference between eGFR and rGFR was defined as the absolute value of the difference. The difference between eGFR and rGFR was regressed against the average of eGFR and rGFR. The bias for eGFR was expressed as the area between the regression line and a common distance along the zero difference line. Ninety-five percent limits of agreement were then constructed around this linear regression line. The precision was expressed as the width between the 95% limits of agreement. Accuracy was measured as the percentage of estimated GFR not deviating more than 15%, 30% and 50% from the rGFR.

Quantitative variables were described as mean±SD or median. Because of skewed distribution, the Spearman correlation and linear regression were used to describe the relationship of eGFR and rGFR. The Wilcoxon signed-ranks test method was used to compare the difference or absolute difference between eGFRs and rGFR in each stage of CKD. The Kruskal–Wallis method was used to compare the difference and absolute difference of eGFR in each stage of CKD.

The accuracies of eGFR among stages of CKD, as well as accuracy of eGFR in each stage of CKD were compared using chi-square test; $P<0.05$ was considered to be statistically significant. All statistics were performed using SPSS software (version 11, SPSS, Chicago IL, USA) and Medcalc for Windows (version 4.3, Medcalc software, Mariakerke, Belgium).
Accuracy of both gGFR and c-aGFR expressed as percentages of cases within ±15, ±30 and ±50% of rGFR in each stage of CKD were analysed. Generally, c-aGFR had higher accuracies compared with gGFR in each stage of CKD in 15, 30 and 50% accuracy. The 15% agreement in CKD stages 1–5 were 70, 69.4, 54.9, 42.2 and 27.9% for gGFR and 82.5, 91.1, 73.2, 58.7 and 59.0% for c-aGFR, respectively. The chi-square test showed that the 30% accuracy was significantly different in stages 2–5 (chi-square test, \( P < 0.05 \)); some improvement was obtained for c-aGFR over gGFR in CKD stage 1 without statistical significance. c-aGFR also made some improvement in ±15% and ±50% accuracy over gGFR (Table 2).

Discussion

This paper is mainly a comparison of the different GFR methodologies. In the study of Itoh et al [7], the renal dynamic imaging method that measured GFR was far from satisfactory, and even less valuable than creatinine clearance (Cr). Pcr-based GFR equations take into account age, gender and race, and allow a more reliable GFR estimation compared with Cr.

In our previous work, the abbreviated MDRD equation was modified to make it suitable for Chinese patients of CKD. The modified abbreviated MDRD equation achieved considerable performance improvement compared with the original [13].

Our hypothesis was that, with the improvement of Pcr-based GFR estimation, the renal dynamic imaging would become more unreliable when compared with the Pcr-based equation. To clarify which method outperformed the other, the performances of the modified abbreviated MDRD equation and the modified Gate’s method in GFR estimation were compared. The modified Gate’s method showed higher difference and absolute difference, and lower precision and accuracy than the modified abbreviated MDRD equation. In each CKD stage, although both methods estimating GFR had negative bias in CKD stage 1, and positive bias in CKD stages 3–5, the performance of the modified abbreviated MDRD equation was significantly better than that of modified Gate’s method.

The generally accepted gold standard for GFR estimation was the inulin clearance, but it was

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<th>gGFR</th>
<th>c-aGFR</th>
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<tr>
<td>(ml/min/1.73 m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b (95% CI)</td>
<td>16.92</td>
<td>11.56 (9.44, 13.67)</td>
</tr>
<tr>
<td>m (95% CI)</td>
<td>0.70 (0.65, 0.75)</td>
<td>0.76 (0.73, 0.79)</td>
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<tr>
<td>r (95% CI)</td>
<td>0.81</td>
<td>0.90</td>
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<tr>
<td>Median of difference (25%, 75% percentile)</td>
<td>2.18</td>
<td>-0.03*</td>
</tr>
<tr>
<td>(ml/min/1.73 m²)</td>
<td>(−10.06, 13.61)</td>
<td>(−9.33, 7.69)</td>
</tr>
<tr>
<td>Median of absolute difference (25%, 75% percentile)</td>
<td>12.55 (4.67, 22.02)</td>
<td>8.35* (3.26, 16.34)</td>
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expensive, time-consuming to measure and was not routinely used in clinical practice. Measurement of radioactive-labelled tracer clearance after a single injection has emerged as an alternative to inulin clearance. Among the radio-labelled markers, $^{99m}$Tc-DTPA is relatively inexpensive, convenient to prepare, provides a low radiation dose to patients and can be used for GFR measurement. It has been shown that multiple plasma samples method for GFR determination following a single injection of $^{99m}$Tc-DTPA was identical to inulin clearance [17,18]. Research indicated that the dual blood sampling method significantly correlated with the multiple blood sampling method ($R = 0.996$, standardized estimation error was 2.8 ml/min) [19] and was used as reference GFR in clinical trials as recommended by the Nephrology Committee of Society of Nuclear Medicine [14]. Thus, it was chosen as reference standard in our study.

There are a variety of sources of errors in the estimation of GFR using the modified Gate’s method. The most important, in our opinion, was that the modified Gate’s method was derived from an empirical equation obtained using the measured creatinine clearance (Ccr) as reference GFR, to yield total and separate kidney clearance [1]; because of the well-known pitfalls of Ccr, the Gate’s method inherited inevitable shortcomings of creatinine clearance. We presume that the Gate’s method can be improved if a more proper reference GFR method is used instead of Ccr in prediction of total GFR.

Moreover, some unwanted factors and technical problems were sources of errors in assessing fractional renal uptake from the modified Gate’s method. First, the protein binding can cause substantial errors when $^{99m}$Tc-DTPA is used to measure GFR. Some studies reported that 5–10% of the $^{99m}$Tc-DTPA was plasma protein bounded, resulting in underestimation of true GFR of about 10%; the higher the true GFR, the more the differences [20]. That was because the unbounded activity is excreted more rapidly when GFR is high, and the fraction of residual bounded activity in the blood increases more rapidly, which will give a relatively lower GFR. However in CKD stages 3–5, the influence may be partly masked by the low rGFR values. The influence of plasma protein bind on
rGFR measurement by the dual blood sampling method has been corrected as described previously [15]. Background subtraction was another source of error. In the modified Gate's method, the ROIs were drawn for the kidneys, and the semi-lunar background area around the lower, outer renal margins and 1 min radial activity counts in each ROI were determined 1 min after injection. Counts in ROI included kidneys and perirenal soft tissue, and counts in the renal ROI should be corrected for background count and soft-tissue attenuation to assess true renal accumulation. Previous research [21] showed that liver and spleen uptake were relatively higher in advanced renal insufficiency. Counts in each kidney ROI probably included counts from liver and spleen, while the inferior perirenal background ROI did not include counts from liver and spleen, which underestimated counts from true background, and led to the bias for overestimating GFR at CKD stages 3–5. Some studies reported that if background was subtracted by a sophisticated correction method, a better GFR could be obtained [22–24].

Renal depth was an important variable in the modified Gate's algorithm, which was estimated by an empirical equation of Tonnesen et al. [25]. The authors measured the kidney depth by ultrasound, and made a regression of kidney depth against body weight and height. Because the empirical equation of Tonnesen et al. [25] was derived from Western individuals, it might not be suitable for all subjects, and the variability of renal depth in different individuals may cause substantial estimation errors of gGFR, such as in too thin or too fat subjects or children. Recently, Taylor et al. [26] reported that the equations measuring renal depth by transmission CT appear to give more accurate estimates of renal depth compared with equations of Tonnesen et al., and may improve the reliability of GFR estimation.

The linear attenuation coefficient for Tc-99m in water is 0.153 cm−1; however, the effective attenuation coefficient of Tc-99m in soft-tissue is lower because of the presence of scattering photons. Some studies [27–29] report that the effective attenuation coefficient in soft-tissue ranges from 0.10 to 0.14 cm−1. In the Gate's algorithm, a coefficient of 0.153 cm−1 was used to correct for Tc-99m attenuation in soft-tissue, which could introduce systemic error.

GFR measurement by the modified Gate's method is based on the percent total renal uptake of 99mTc-DTPA for 1 min from 2 to 3 min after the injection [1]. Uptake of 99mTc-DTPA during the first few minutes is GFR times the integral of plasma concentration [P(t)] in this time interval. During the first few minutes after injection, P(t) might be more determined by 99mTc-DTPA distribution than by renal clearance. Thus, the uptake of 99mTc-DTPA may reflect tracer distribution more than renal clearance. We regressed gGFR, rGFR and difference between gGFR and rGFR against the 99mTc-DTPA distribution volume (calculated as 20% body weight) separately, to evaluate if gGFR or the difference were significantly correlated with the 99mTc-DTPA distribution volume, but no correlation was found. So we could not confirm the estimate error for 99mTc-DTPA distribution volume on GFR determination in the modified Gate's method.

Finally, there might be other factors that influenced the accuracy of uptake calculations, such as, age, shape of kidneys, etc., which caused obvious estimation errors of gGFR.

In conclusion, the modified Gate's method is undoubtedly an important method in unilateral renal function measurement. But our results implied that its performance in total GFR estimation was not better than the modified abbreviated MDRD equation in our patient group. So, it was suggested that GFR estimated by the current modified Gate's method could not be used as a marker of treatment effectiveness or a monitor of GFR change in clinical trials. We presume that the dynamic renal imaging method for estimation of GFR can be improved by using proper reference GFR, as well as more adequate background subtraction and soft-tissue attenuation correction, in a relatively larger sample size.

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