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Prediction of two-sample ^{99m}Tc-diethylene triamine pentaacetic acid plasma clearance from single-sample method

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Objectives: To develop an equation to predict dual plasma sample method (DPSM) ^{99m}Tc-diethylene triamine pentaacetic acid (^{99m}Tc-DTPA) plasma clearance from single plasma sample method (SPSM), and to clarify the condition in which DPSM can be substituted by SPSM in measurement of glomerular filtration rate (GFR). ***Methods:*** Patients with chronic kidney disease (CKD) were selected. Watson modified Christensen and Groth equation was used to calculate ^{99m}Tc-DTPA plasma clearance by SPSM (sGFR). The equation recommended by the Nephrourology Committee of the Society of Nuclear Medicine was used to calculate ^{99m}Tc-DTPA plasma clearance by DPSM (tGFR) in each patient. The difference between sGFR and tGFR was expressed as percent of the average of these two methods, and tGFR was predicted from sGFR. Plasma creatinine was measured by the kinetic picrate method, and GFR estimated by abbreviated modification of diet in renal disease (MDRD) equation (aGFR) and Cockcroft-Gault equation (cGFR) were evaluated as criteria in selection of DPSM and SPSM. ***Results:*** Three hundred and sixty-nine patients with CKD were selected (208 male and 161 female). The average age and body weight were 51.4 ± 15.5 years and 67.2 ± 12.5 kg, respectively. The causes of CKD were glomerular disease, renal arterial stenosis, chronic tubulointerstitial disease, and other causes or causes unknown. The average tGFR was 62.9 ± 36.5 ml/min/1.73 m^2, ranging from 1–180 ml/min/1.73 m^2. sGFR was significantly correlated with tGFR ($r = 0.9194$, $p < 0.001$), but widely scattered when tGFR <30 ml/min/1.73 m^2; in contrast, then tGFR was ≥30 ml/min/1.73 m^2, the difference was constant (−1.1%, 95% confidence interval −18.3%, 16.1%), and tGFR could be predicted from sGFR using the equation: predicted tGFR (ml/min/1.73 m^2) = 7.4244 + 0.7318 × sGFR + 0.0022 × sGFR^2 ($n = 299$, $r^2 = 0.9428$, $p < 0.001$), and the difference decreased to 0.1%, 95% confidence interval (−15.8%, 16.0%). aGFR was better than cGFR in diagnosis of tGFR <30 ml/min/1.73 m^2, the diagnostic sensitivity of a cut off value of aGFR = 45 ml/min/1.73 m^2 was 91.8%, and recommended as a criterion in the selection of DPSM and SPSM. ***Conclusion:*** When GFR ≥30 ml/min/1.73 m^2, tGFR can be predicted from sGFR, which will simplify the reference GFR measurement in clinical trials. sGFR becomes widely scattered when tGFR is less than 30 ml/min/1.73 m^2. To obtain reliable reference GFR values, it is recommended that DPSM be used in clinical trials when aGFR is less than 45 ml/min/1.73 m^2.

Key words: glomerular filtration rate, ^{99m}Tc-DTPA, plasma clearance, single plasma sample method, dual plasma sample method

INTRODUCTION

RENAL CLEARANCE of exogenous inulin has been commonly used as the gold standard of glomerular filtration rate (GFR) in clinical trials,[1,2] but the procedure is complex and seldom used because of the need for continuous venous infusion of inulin, multi-blood sampling and urine

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collection. Some radio-labeled markers (i.e., ^{99m}Tc-diethylene triamine pentaacetic acid, ^{99m}Tc-DTPA; ^{51}Cr-ethylene diamine tetraacetic acid, ^{51}Cr-EDTA) which are almost completely filtrated by the glomeruli, are not secreted or reabsorbed by renal tubules, and are not eliminated through extra-renal organs, can replace inulin in GFR measurement.[3–5] Among the radio-labeled markers, ^{99m}Tc-DTPA is cost effective, is convenient to prepare, has low radiation to patients, and its plasma clearance is commonly used to measure GFR.

^{99m}Tc-DTPA plasma clearance measured by multiple plasma sample method (MPSM) is almost identical to inulin renal clearance,[6–8] but it is complex because of the need of more blood sample collection and computer software. To simplify the procedure in calculation of ^{99m}Tc-DTPA plasma clearance, dual plasma sample method (DPSM) and single plasma sample method (SPSM) have been compared with MPSM. ^{99m}Tc-DTPA plasma clearance by DPSM is significantly correlated with that by MPSM,[9] and can be used if special accuracy is needed.[10] SPSM is more convenient than DPSM, but in patients with advanced renal failure, the result of SPSM becomes unreliable.[9,11–13] It is recommended that DPSM be used when the true GFR is less than 30 m*l*/min/1.73 m^2.[3]

But for a given patient, when his (her) true GFR is not known before measurement, the researcher has to decide which method to use, SPSM or DPSM. Plasma creatinine (Pcr) level is one of the most commonly used indices in clinical practice to estimate GFR, and a previous study[3] showed that Pcr level of 2 mg/d*l* corresponded to a true GFR level of 30 m*l*/min/1.73 m^2, and could be used as a cut off value to aid in the selection of SPSM and DPSM. But as the Pcr level can be influenced by multiple factors,[14,15] in elderly patients, especially those with muscular atrophy, a Pcr level of less than 2 mg/d*l* may represent a true GFR level of less than 30 m*l*/min/1.73 m^2, and SPSM applied to these patients may report unreliable results.

In the current study, DPSM and SPSM were compared in the measurement of ^{99m}Tc-DTPA plasma clearance, and GFR estimated from Pcr based equations was evaluated as a criterion for the selection of DPSM and SPSM.

MATERIALS AND METHODS

Patients

Patients with chronic kidney disease (CKD) aged more than 18 years old from Peking University First Hospital from June 2003 to December 2004 were selected. CKD was diagnosed and classified according to Kidney Disease Outcome Quality Initiatives (K/DOQI) clinical practice guideline.[16] Patients with acute kidney function deterioration, edema, skeletal muscle atrophy, pleural effusion or ascites, malnutrition, amputation, heart failure, or ketoacidosis were excluded. Patients who were currently taking cimetidine or trimethoprim were also excluded. Sex, age, body height, and body weight of the patients were recorded.

Medicine and instrument

^{99m}Tc-DTPA (purity 95%) was obtained from Beijing Senke Company. Plasma radioactivity (cpm) was measured with HY-901 multi-function well counter from Beijing Sixin Company. Injected dose (kcps) of ^{99m}Tc-DTPA was measured by Millennium ^{TM}MPR SPECT from General Electric Medical System, and converted to value of HY-901 multi-function well counter (cpm) according to the standardized conversion curve.

^{99m}Tc-DTPA plasma clearance measured by DPSM and SPSM

(1) Patients were requested to drink 300–500 m*l* water after breakfast, 20 minutes before the measurement. Radioactivity of the syringe containing ^{99m}Tc-DTPA was measured before injection. A bolus of about 185 MBq ^{99m}Tc-DTPA was injected into the patients' forearm. Residual radioactivity of the syringe was measured again, and injected dosage of drug was calculated. Heparin anticoagulated blood samples were taken 2 and 4 hours after injection from the contralateral forearm.

(2) ^{99m}Tc-DTPA plasma clearance by DPSM (tGFR) was calculated according to the following equation[10]:

$$\text{tGFR (m}l\text{/min)} = \{D \ln (P_1/P_2)/(T_2 - T_1) \exp [(T_1 \ln P_2) - (T_2 \ln P_1)]/(T_2 - T_1)\} \times 0.93$$

Where D: dose of drug injected;

T_1: time of first blood sample (about 2 hours);

P_1: plasma activity at T_1;

T_2: time of second blood sample (about 4 hours);

P_2: plasma activity at T_2.

Unit for D, P_1 and P_2 was cpm/min/m*l*; unit for T_1, T_2 was min.

(3) ^{99m}Tc-DTPA plasma clearance by SPSM (sGFR) was calculated according to Watson modified Christensen and Groth equation[17]:

$$\text{sGFR} = [-b + (b^2 - 4ac)^{1/2}]/2a$$

Where $a = t \times (0.0000017 \times t - 0.0012)$;

$b = t \times (-0.000775 \times t + 1.31)$;

$c = \text{ECV} \times \ln(\text{ECV}/Vt)$;

ECV (extracellular volume in m*l*) = 8116.6 × surface area (m^2) – 28.2;

Vt = tracer distribution volume at time t, m*l*;

t = the time when blood was sampled (about 4 hours after injection).

(4) The measured tGFR and sGFR were standardized by body surface area (BSA, m^2). BSA was calculated as described by DuBois equation[18]:

$$\text{BSA (m}^2\text{)} = 0.007184 \times \text{body weight (kg)}^{0.425} \times \text{body height (cm)}^{0.725}$$

(5) Decay of radioactivity was corrected according to the following equation:

$$\text{corrected radioactivity} = \text{measured activity} \times \text{Exp}(-\ln(2) \times \text{interval}/6.02)$$

Estimation of GFR from Pcr based equations

Pcr levels were measured by Jaffe's kinetic method with a sample blank on a Hitachi 7600 analyzer (Hitachi, Tokyo, Japan), and calibrated (normal reference range, 0.72–1.48 mg/d*l* or 64–131 μmol/*l*) as described by Zuo et al.[19]

GFR was estimated from abbreviated modification of diet in renal disease (MDRD) equation[20] (aGFR) and modified Cockcroft-Gault equation[20,21] (cGFR).

aGFR (m*l*/min/1.73 m^2)
$= 186 \times [Pcr]^{-1.154} \times [age]^{-0.203} \times [0.742 \text{ if female}]$

cGFR (m*l*/min/1.73 m^2)
$= [(140 - age) \times body\ weight]/(Pcr \times 72) \times 0.84 \times [0.85 \text{ if female}]$

Statistical analysis

Quantitative variables were described as mean ± standard deviation or median. Paired t test, correlation and linear regression were used to describe the relationship of sGFR and tGFR, and second order polynomials to predict tGFR from sGFR. Difference between sGFR and tGFR was expressed as percent of average of sGFR and tGFR. Bland-Altman plot[22] of difference between methods against average of methods was used to express the performance of sGFR and predicted tGFR. Performance of aGFR and cGFR in the diagnosis of tGFR less than 30 m*l*/min/1.73 m^2, which was expressed as the area under the receiver operating curve (ROC), was compared, and optimum cut off value of aGFR or cGFR with sufficient sensitivity was calculated. The results were considered to be significant if the p-value was less than 0.05. MedCalc statistic software 7.6.0.0 (Medcalc software, Mariekerke, Belgium) was used for data analysis.

RESULTS

Three hundred and sixty-nine patients with CKD were selected (208 male and 161 female). The average age and body weight were 51.4 ± 15.5 years and 67.2 ± 12.5 kg, respectively. The causes of CKD were glomerular disease, renal arterial stenosis, chronic tubulointerstitial disease, and other causes or causes unknown. The average tGFR was 62.9 ± 36.5 m*l*/min/1.73 m^2, ranging from 1–180 m*l*/min/1.73 m^2. Detailed demographic characteristics, causes and staging of CKD were listed in Table 1.

Although sGFR was significantly correlated with tGFR ($r = 0.9194$, $p < 0.001$), they were significantly different by paired t test ($p < 0.01$). Bland-Altman plot of difference as percent of average of sGFR and tGFR against average of the two methods showed that the mean difference was –2.5%, 95% confidence interval (–96.6%, 101.6%) (Fig. 1 and Fig. 2). When the average of the two methods was greater than 30 m*l*/min/1.73 m^2, the difference was almost constant [–1.1%, 95% confidence interval (–18.3%, 16.1%)] (Fig. 3); on the other hand, when the average of the two methods was less than 30 m*l*/min/1.73 m^2, the difference was widely scattered.

From 299 patients with tGFR greater than 30 m*l*/min/1.73 m^2, 150 patients were randomly selected, and tGFR was predicted from sGFR ($r^2 = 0.9442$, $p < 0.001$), and the prediction equation was expressed as:

Predicted tGFR (m*l*/min/1.73 m^2)
$= 4.7735 + 0.8235 \times sGFR + 0.0015 \times sGFR^2$

Table 1 General characteristics of enrolled patients

Demographic characteristics	
average age (years)	51.4 ± 15.5
body weight (kg)	67.2 ± 12.5
body height (cm)	166.1 ± 8.5
body surface area (m^2)	1.74 ± 0.19
tGFR (m*l*/min/1.73 m^2)	62.9 ± 36.5
Causes of CKD	
primary or secondary glomerular disease	103 (27.9%)
obstructive kidney disease or renal lithiasis	81 (22.0%)
renal arterial stenosis	31 (8.4%)
chronic tubulointerstitial disease	22 (5.9%)
kidney cystic disease	7 (1.9%)
other causes or causes unknown	125 (33.9%)
CKD stages	
1	79 (21.4%)
2	104 (28.2%)
3	110 (29.8%)
4	44 (11.9%)
5	32 (8.7%)

Abbreviation: tGFR, ^{99m}Tc-DTPA plasma clearance by dual plasma sample method (m*l*/min/1.73 m^2); CKD, chronic kidney disease; ^{99m}Tc-DTPA, ^{99m}Tc-diethylene triamine pentaacetic acid.

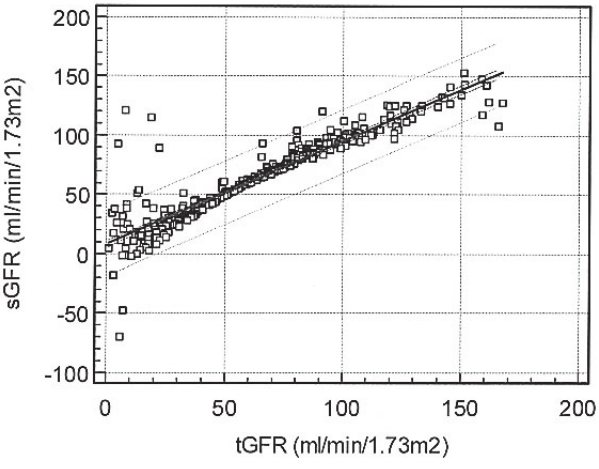

Fig. 1 Scatter plot of sGFR against tGFR. sGFR was significantly correlated with tGFR [r = 0.9194, 95% confidence interval (0.9019, 0.9339), p < 0.0001]. sGFR, body surface area standardized ^{99m}Tc-DTPA plasma clearance by single plasma sample method (m*l*/min/1.73 m^2); tGFR, body surface area standardized ^{99m}Tc-DTPA plasma clearance by two plasma sample method (m*l*/min/1.73 m^2); DTPA, ^{99m}Tc-diethylene triamine pentaacetic acid.

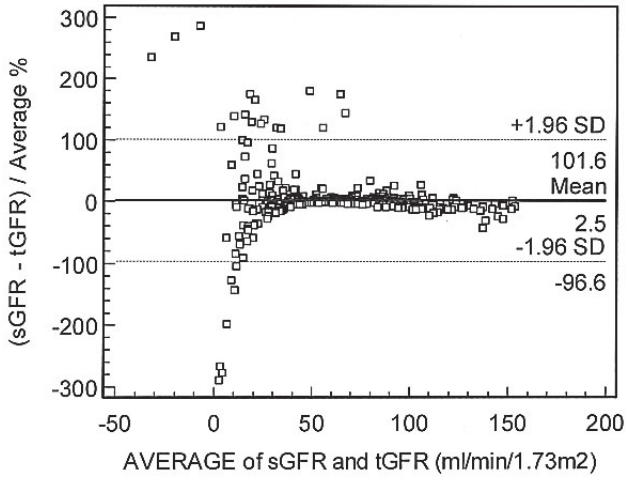

Fig. 2 Bland-Altman plot of difference as percent of average of sGFR and tGFR against average of the two methods. The mean difference was −2.5%, 95% confidence interval (−96.6%, 101.6%). When average of the two methods was greater than 30 ml/min/1.73 m^2, the difference as percent of average is almost constant. sGFR, body surface area standardized ^{99m}Tc-DTPA plasma clearance by single plasma sample method (ml/min/1.73 m^2); tGFR, body surface area standardized ^{99m}Tc-DTPA plasma clearance by two plasma sample method (ml/min/1.73 m^2); DTPA, ^{99m}Tc-diethylene triamine pentaacetic acid.

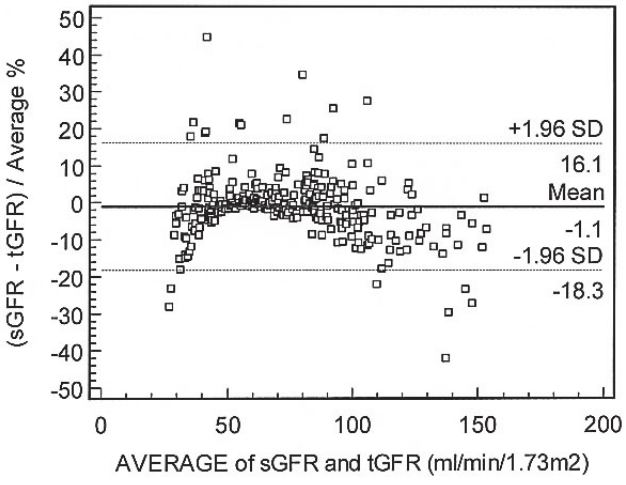

Fig. 3 Bland-Altman plot of difference as percent of average of sGFR and tGFR against average of the two methods in tGFR range of greater than 30 ml/min/1.73 m^2. The mean difference was −1.1%, 95% confidence interval (−18.3%, 16.1%). sGFR, body surface area standardized ^{99m}Tc-DTPA plasma clearance by single plasma sample method (ml/min/1.73 m^2); tGFR, body surface area standardized ^{99m}Tc-DTPA plasma clearance by two plasma sample method (ml/min/1.73 m^2); DTPA, ^{99m}Tc-diethylene triamine pentaacetic acid.

This equation was applied to all patients with tGFR >30 ml/min/1.73 m^2 to predict tGFR. Further Bland-Altman plots of difference as percent of average of sGFR and predicted tGFR, against average of the two methods were

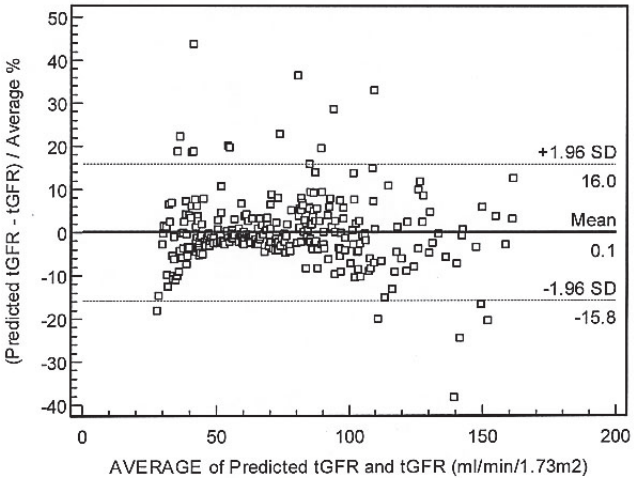

Fig. 4 Bland-Altman plot of difference as percent of average of predicted tGFR and tGFR against average of the two methods in tGFR range of greater than 30 ml/min/1.73 m^2. Predicted tGFR (ml/min/1.73 m^2) = 4.7735 + 0.8235 × sGFR + 0.0015 × $sGFR^2$ (n = 150, r^2 = 0.9442, p < 0.001). The mean difference was 0.1%, 95% confidence interval (−15.8%, 16.0%) when the equation was applied to all the 299 patients with tGFR greater than 30 ml/min/1.73 m^2. For more precise tGFR prediction, all patients with tGFR greater than 30 ml/min/1.73 m^2 were included and the equation rewritten as predicted tGFR (ml/min/1.73 m^2) = 7.4244 + 0.7318 × sGFR + 0.0022 × $sGFR^2$ (n = 299, r^2 = 0.9428, p < 0.001). sGFR, body surface area standardized ^{99m}Tc-DTPA plasma clearance by single plasma sample method (ml/min/1.73 m^2); tGFR, body surface area standardized ^{99m}Tc-DTPA plasma clearance by two plasma sample method (ml/min/1.73 m^2); DTPA, ^{99m}Tc-diethylene triamine pentaacetic acid.

made. The difference decreased dramatically from −1.1% to 0.1% (Fig. 3 and Fig. 4).

For more precise tGFR prediction, all patients with tGFR greater than 30 ml/min/1.73 m^2 were included and the equation was rewritten as follows (n = 299, r^2 = 0.9428, p < 0.001):

Predicted rGFR (ml/min/1.73 m^2)

= 7.4244 + 0.7318 × sGFR + 0.0022 × $sGFR^2$

Receiver operating characteristic (ROC) curves comparing aGFR and cGFR for diagnosis of tGFR less than 30 ml/min/1.73 m^2 were made. The areas under the curve for aGFR were significantly higher than those for cGFR (0.937 vs. 0.922, p < 0.05) (Fig. 5). The sensitivity and specificity of aGFR for diagnosis of tGFR less than 30 ml/min/1.73 m^2 were listed in Table 2, the diagnostic sensitivity of aGFR less than 45 ml/min/1.73 m^2 for diagnosis of tGFR less than 30 ml/min/1.73 m^2 was 91.8%.

Percent difference between predicted tGFR and tGFR, against aGFR was plotted. In aGFR range of greater than 45 ml/min/1.73 m^2, the difference was 1.0% ± 10.8%; whereas, in aGFR range of less than 45 ml/min/1.73 m^2, the difference not only increased to 12.6% ± 62.6%, but also scattered (Fig. 6).

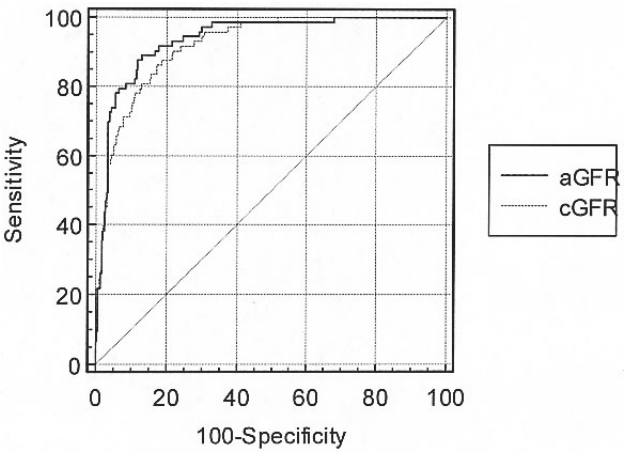

Fig. 5 Receiver operating characteristic (ROC) curves comparing abbreviated modification of diet in renal disease (MDRD) equation and Cockcroft-Gault equation for prediction of tGFR less than 30 ml/min/1.73 m^2. The area under the curve was 0.937 (95% confidence interval from 0.907 to 0.960) for aGFR, which is significantly higher than that for cGFR (0.922, 95% confidence interval from 0.889 to 0.947). aGFR, GFR predicted by abbreviated MDRD equation; cGFR, GFR predicted by modified Cockcroft-Gault equation.

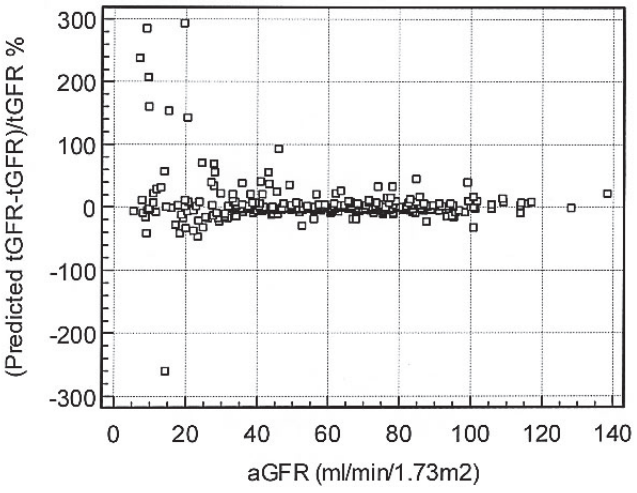

Fig. 6 Plotting percent difference between predicted tGFR and tGFR against aGFR. In aGFR range of greater than 45 ml/min/1.73 m^2, the difference was 1.0% ± 10.8%; whereas, in aGFR range of less than 45 ml/min/1.73 m^2, the difference not only increased to 12.6% ± 62.6%, but also scattered.

Table 2 Sensitivity and specificity of abbreviated MDRD equation in the diagnosis of tGFR less than 30 ml/min/1.73 m^2

Cut off value of aGFR (ml/min/1.73 m^2)	Sensitivity (%)	Specificity (%)
20	46.6	97.2
25	58.9	96.5
30	72.6	95.8
35	79.5	92.3
40	86.3	88.2
45	91.8	80.1
50	94.5	73.2

Abbreviation: MDRD, modification of diet in renal disease; tGFR, body surface area standardized ^{99m}Tc-DTPA plasma clearance by dual plasma sample method (ml/min/1.73 m^2); aGFR, GFR predicted by abbreviated MDRD equation; ^{99m}Tc-DTPA, ^{99m}Tc-diethylene triamine pentaacetic acid.

DISCUSSION

Compared with inulin clearance, radionuclide agents' clearance has many advantages, and ^{51}Cr-EDTA and ^{99m}Tc-DTPA are among the most commonly used radionuclide tracers for measuring GFR.[5] Studies have shown that their renal clearance correlates well with inulin clearance, the ^{99m}Tc-DTPA to inulin ratio was 0.97.[7] Further, plasma clearance of ^{99m}Tc-DTPA correlates well with inulin clearance (standardized estimation error is 3.5 ml/min).[7,8] Plasma nuclide clearance assessed by MPSM is considered the "gold standard" in GFR measurement.

Although the method of ^{99m}Tc-DTPA plasma clearance after single injection is more convenient than that of inulin clearance, it is still cumbersome in practice. Therefore, alternative methods are routinely used, such as the DPSM and SPSM, which were derived from the empirical analysis of the relationship between the reference GFR and the volume of distribution and plasma concentration at sample time.[12,13] The result of DPSM is significantly correlated with that of MPSM (r = 0.996, standardized estimation error is 2.8 ml/min),[9] and recommended by the Nephrourology Committee of the Society of Nuclear Medicine when special accuracy is needed (i.e., for investigational purpose).[10]

The reference GFR measurement will be greatly simplified if DPSM can be substituted by SPSM. In the current study, sGFR and tGFR were compared; an equation was developed to predict tGFR from sGFR, and the condition in which tGFR could be predicted was given.

As to SPSM, several equations can be used to calculate sGFR.[17,23,24] A previous study comparing SPSM and MPSM showed that sGFR calculated by different SPSM equations was consistent.[11] In the current study, Watson modified Christensen and Groth formula was used to calculate sGFR.[17]

Our results showed that when tGFR was greater than 30 ml/min/1.73 m^2, sGFR was closely correlated with tGFR, and tGFR could be accurately predicted from sGFR. The co-efficiency of determination for the equation was 0.9428 ($p < 0.001$). The prediction equation would simplify reference GFR measurement in clinical trials.

The diagnosis of true GFR less than 30 ml/min/1.73 m^2 could be made according to Pcr based GFR estimating equations, and selection of SPSM and DPSM could be made according to the estimated GFR. Among the equations, MDRD equations were published in 1999,[25] and

considered the best GFR estimating equation. A lot of evidence shows that MDRD equations are more reliable than other Pcr based equations, such as Cockcroft-Gault equation, or creatinine clearance in prediction of true GFR.[16,26] The abbreviated MDRD equation is the short form of MDRD equations published in 2000,[20] which includes only Pcr, age and sex, but remains as accurate as the non abbreviated ones. Although evidence shows that abbreviated MDRD equation almost always under-estimates GFR in normal population and patients of CKD with normal GFR,[19,27,28] it performs well in true GFR range of less than 90 ml//min/1.73 m^2, and can be used in the selection of SPSM and DPSM.

Our study showed that the performance of abbreviated MDRD equation was better than the Cockcroft-Gault equation in diagnosis of tGFR <30 ml//min/1.73 m^2. Because of the importance of an accurate reference GFR value to a clinical trial, a cut off value of aGFR = 45 ml//min/1.73 m^2 or higher was recommended. If aGFR is greater than 45 ml//min/1.73 m^2, DPSM can be substituted by SPSM. A higher cut off value will prevent the use of SPSM in patients with tGFR value lower than 30 ml//min/1.73 m^2.

Although sGFR was significantly correlated with tGFR, sGFR was widely scattered when tGFR <30 ml//min/1.73 m^2, which was consistent with the literature.[9,11,16] Li et al.[11] had summarized the reasons for the inaccuracy of SPSM. First, extra-renal elimination of ^{99m}Tc-DTPA in patients with GFR <30 ml//min may be responsible because of the prolonged time to reach equilibrium; second, arterio-venous concentration difference due to the change in forearm blood flow may cause variation of plasma radioactivity; and finally, when the value of GFR is small, a small absolute difference causes a large relative error (percent difference). It is recommended that a blood sample be taken 24 hours after injection to correct this problem.

In conclusion, our results indicated that when tGFR is ≥30 ml//min/1.73 m^2, tGFR by DPSM can be predicted from sGFR by SPSM, which simplifies reference GFR measurement in clinical trials. GFR predicted by abbreviated MDRD equation can be used for selection of DPSM and SPSM. To increase the sensitivity of abbreviated MDRD equation in the diagnosis of tGFR <30 ml//min/1.73 m^2, the cut off value of aGFR = 45 ml//min/1.73 m^2 or higher was recommended.

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