Evaluation of Glomerular Filtration Rate by Camera-Based Method in Both Children and Adults

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We describe a method to evaluate glomerular filtration rate (GFR) in both children and adults using ^{99m}Tc-diethylenetriamine pentaacetic acid (DTPA) and a gamma camera. **Methods:** Renal scintigraphy with ^{99m}Tc-DTPA was performed in 40 children and 92 adults with various degrees of renal function. The percent renal uptake at 2–2.5 min after tracer arrival in the kidney was determined with background subtraction and correction for soft-tissue attenuation and was correlated by linear regression analysis with GFR measured from two blood samples. A perirenal region of interest was used for background subtraction. Renal depth was computed using the equations determined or validated on the basis of CT measurements, and the attenuation coefficient was set at 0.12. The obtained regression equation was used to predict GFR. Renal function was also assessed by the Gates' method. **Results:** Percent renal uptake was closely correlated with GFR normalized for body surface area in all patients ($y = 15.958x - 2.94$; $r = 0.939$). GFR was successfully predicted using the regression equation in both children and adults. Gates' method severely overestimated GFR in children and provided less accurate values even in adults than our method. **Conclusion:** The method presented here requires neither blood sampling nor additional imaging and allows estimation of GFR in both children and adults.

Key Words: glomerular filtration rate; technetium-99m-diethylenetriamine pentaacetic acid; children; adults; gamma camera

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Estimation of glomerular filtration rate (GFR) is a major role of renal scintigraphy with ^{99m}Tc-diethylenetriamine pentaacetic acid (DTPA) and several methods have been proposed (*1–13*). Among them, camera-based methods without blood or urine sampling have been used in children (*6–9*) as well as in adults (*10–13*). These methods are convenient, and the omission of blood sampling seems to be beneficial, especially in children.

The camera-based methods are usually applied to quantitative evaluation of renal function in only one of the two groups (children or adults), and the use of two different techniques is required in nuclear medicine departments to which both children and adults are referred. In addition to operator trouble, this may cause problems in the long-term observation of pediatric patients as they grow into adolescents. Switching from a pediatric method to an adult method may induce some discontinuity in serial measurements of renal function.

The aim of this study was to develop a camera-based method to estimate GFR in both children and adults. Such a method would add convenience to the evaluation of renal function in routine clinical practice.

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MATERIALS AND METHODS

Subjects

In this study, 132 patients referred for renal scintigraphy to evaluate various renal disorders were examined. They included 40 pediatric patients (22 males, 18 females; age range 0–14 yr; mean age 5.8 ± 4.4 yr). Six patients were younger than 1 yr, and the youngest patient was 8 mo. The other 92 patients were adults (50 males, 42 females; age range 16–87 yr; mean age 51.7 ± 16.9 yr). Three children and 9 adults had unilateral kidney, the others had bilateral kidneys. Before the examination, the purpose and methods of the study were explained to the patients or their parents and consent was obtained.

Imaging Procedures

To provide adequate hydration, adult patients were encouraged to drink 250 ml of water 30 min before the examination. In children, hydration was attained by drinking or drip infusion. The patient was placed on the imaging table in the supine position. Immediately after the bolus injection of ^{99m}Tc-DTPA, posterior dynamic imaging was performed for 30 min. Eighty 3-sec frames were acquired in a 128 × 128 matrix, followed by the collection of 52 frames at a rate of 30 sec/frame. Appropriate zooming was applied to the imaging of children. The injected dose was determined on the basis of body surface area (BSA) and 200 MBq/m^2 was given. A gamma camera (GCA901A/WG; Toshiba, Tokyo, Japan) equipped with a low-energy, general-purpose collimator interfaced to a minicomputer (GMS5500, Toshiba) was used.

The injected dose was measured with the same gamma-camera system. A hollow paper box 20 cm in height was put on the imaging table above the collimator. The syringe was placed on the paper box before and after injection, and data were acquired for 15 sec each. The camera system used has an intrinsic circuit for deadtime correction, and the proportionality between activity in the syringe and counting rate has been confirmed in the range of counting rates observed in this study.

Venous blood samples were obtained from the arm contralateral to the injection site at 2 and 3 hr after the injection of ^{99m}Tc-DTPA. The sample was centrifuged, and plasma activity was measured in a well counter.

Reference Method

The clearance method using blood samples taken at 2 and 3 hr postinjection was used as a reference to measure actual GFR (*14*). GFR was calculated by the following equation:

$$\text{GFR (ml/min)} = I \cdot \lambda / A, \qquad \text{Eq. 1}$$

where I is injected dose, λ is the exponential slope of the clearance curve and A is initial plasma tracer concentration obtained by extrapolation of the clearance curve.

The measured GFR was normalized for BSA and was expressed as ml/min/1.73 m^2. BSA was computed by the following equation (*15*):

$$BSA = 0.024265 \cdot BW^{0.5378} \cdot BH^{0.3964}, \qquad \text{Eq. 2}$$

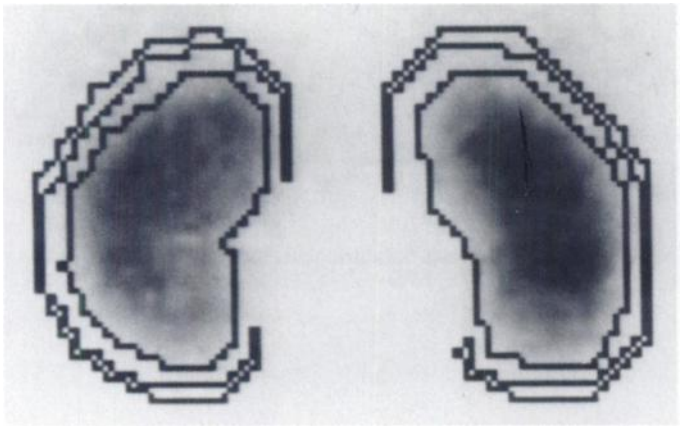

FIGURE 1. Regions of interest placed for kidneys and perirenal background regions.

where BW is body weight in kilograms and BH is body height in centimeters.

Camera-Based Method

The regions of interest (ROIs) were manually drawn for the kidneys and perirenal background areas (Fig. 1), and counts in each ROI were determined 2–2.5 min after tracer arrival in the kidney. The perirenal background ROI was set around each kidney, excluding the area facing the renal hilus to allow the use of the same ROIs in producing renograms. If the area facing the renal hilus is included in the background ROI, a large amount of radiotracer excreted in the renal pelvis may appear in the ROI at the late phase, resulting in overestimation of background activity. The counts per pixel in the background ROI were multiplied by the number of pixels in the corresponding kidney ROI and subtracted from counts in the kidney ROI to obtain the background-subtracted renal count.

Renal depth was estimated in children using the equation described by Raynaud et al. (*16*) and in adults using the equation presented by Taylor et al. (*17*):

0–9 yr	$d = 2.366 + 0.083 \cdot BW - 0.00281 \cdot BH$
10–15 yr	$d = 3.686 + 0.028 \cdot BW - 0.00248 \cdot BH$
≥16 yr	(right) $d = 15.13 \cdot BW/BH + 0.022 \cdot A + 0.077$
	(left) $d = 16.17 \cdot BW/BH + 0.027 \cdot A - 0.94$

where d is renal depth in centimeters and A is age in years. The equations of Raynaud et al. (*16*) provide the same depths for the right and left kidneys. Based on the calculated renal depth, the background-subtracted renal count (Cb) was corrected for soft-tissue attenuation assuming the attenuation coefficient at 0.12/cm:

$$Ca = Cb/\exp(-0.12 \cdot d),$$

where Ca is renal counts after attenuation correction.

The injected count was assessed by subtracting the count for the postinjection syringe from that for the preinjection syringe. These counts were corrected for decay to the injection time before subtraction. Both the attenuation-corrected renal count and injected count were converted to the unit of counts per minute. The percentage renal uptake at 2–2.5 min (% uptake) was computed as follows:

$$\%\ \text{uptake} = (rCa + lCa)/Ci,$$

where rCa and lCa are attenuation-corrected renal counts for the right and left kidneys, respectively, and Ci is injected count.

The percentage uptake was correlated with GFR measured by the reference method and normalized for BSA. Linear regression analysis was performed by the least square method. Then, GFR was predicted using the obtained regression equation and compared with the measured GFR.

Comparison with Gates' Method

GFR was also computed by Gates' method in all patients (*11*). Counts in the kidney ROI at 2–3 min after tracer arrival in the kidney were corrected for background counts and soft-tissue attenuation. Background ROIs were drawn in the portion inferolateral to the kidneys. Renal depth was assessed by the equation of Tonnesen et al. (*18*), and the attenuation coefficient was set at 0.153. The corrected renal count and injected count were substituted in the empiric equation described by Gates, and GFR was calculated. The obtained value was compared with the GFR measured by the reference method.

RESULTS

The GFR measured from two blood samples ranged from 8.3 to 182.5 ml/min/1.73 m^2 in children and from 5.7 to 146.7 ml/min/1.73 m^2 in adults. Correlation between BSA-uncorrected GFR and percent renal uptake at 2–2.5 min postinjection was poor in all patients (Fig. 2). The regression line obtained between BSA-uncorrected GFR and percent uptake in children was obviously different from that obtained in adults. In contrast to BSA-uncorrected GFR, BSA-corrected GFR was closely correlated with percent renal uptake in all patients, including children and adults (Fig. 3) ($y = 15.958x - 2.94$; $r = 0.939$; s.e.e. = 13.89), and this relation seemed to enable estimation of GFR with acceptable accuracy. The GFR predicted using this regression equation was highly correlated with that measured by the reference method in all patients (Fig. 4A). A high correlation was also observed between the predicted and mea-

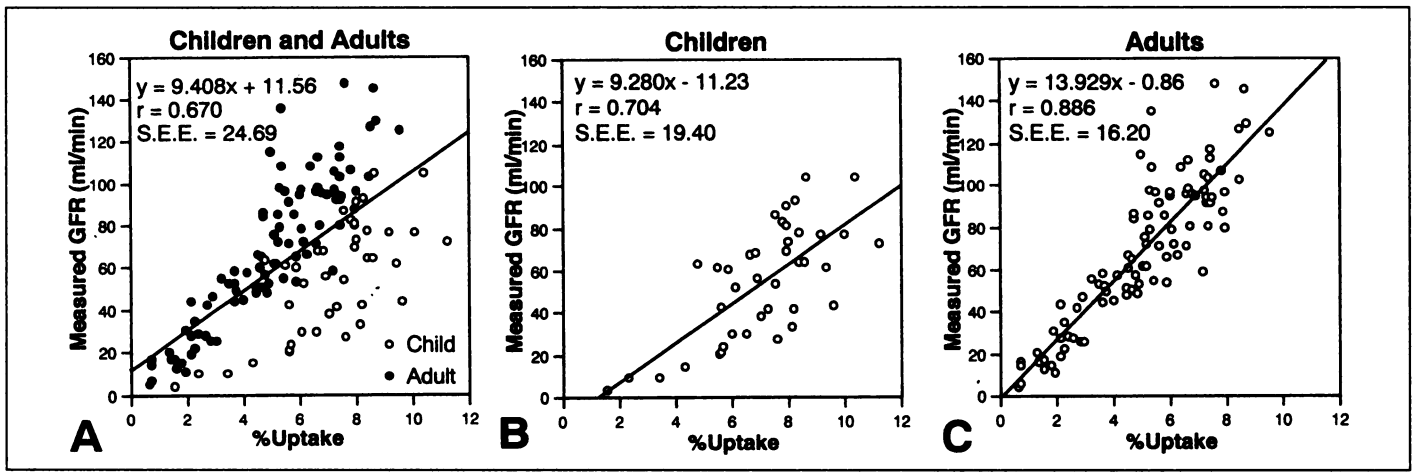

FIGURE 2. Relationship between percent renal uptake and body surface area-uncorrected glomerular filtration rate (GFR) measured by reference method.

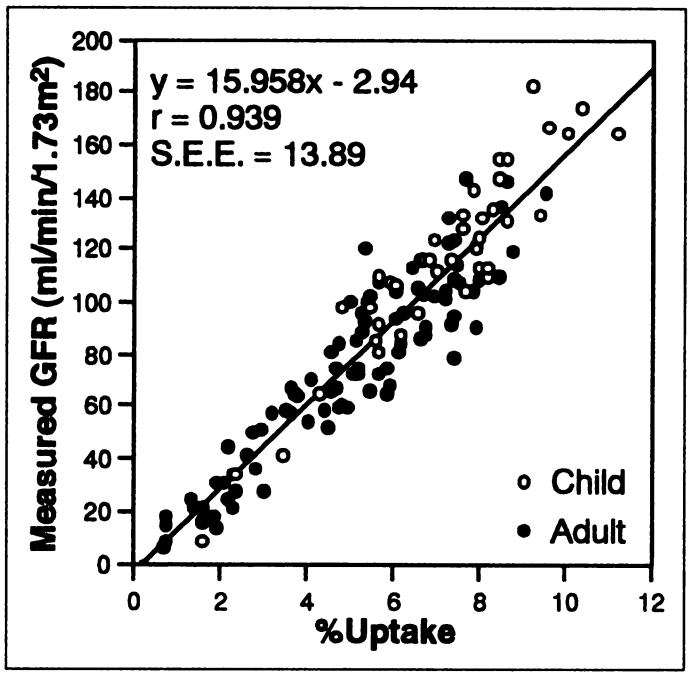

FIGURE 3. Relationship between percent renal uptake and body surface area-corrected glomerular filtration rate (GFR) measured by reference method.

sured GFRs when regression analysis was performed in children (Fig. 4B) and adults (Fig. 4C) separately.

The GFR calculated by Gates' method was plotted against measured GFR (Fig. 5). Gates' method overestimated pediatric GFR severely and showed large variations. It also provided less precise results in adults than the method proposed in this article.

DISCUSSION

Camera-based methods to estimate GFR are simple and suitable for clinical use. Among them, the Gates' method is commercially available and widely used. In adults, the correlation between measured GFR and the GFR calculated by Gates' method in this study was similar to that reported in previous validation studies (*19–21*). Larger errors were observed in children. Gates' method severely overestimated GFR in pediatric patients, and the correlation between the values obtained by the reference method and by Gates' method was much lower in children than in adults.

If it is assumed for the early part of renal scintigraphy with ^{99m}Tc-DTPA that the filtered radiotracer does not leave the kidney and plasma concentration remains constant, renal accumulation at time t (R(t)) is:

$$R(t) = G \cdot P \cdot t, \qquad \text{Eq. 3}$$

where G is BSA-uncorrected GFR and P is plasma concentration.

In a camera-based method without blood sampling, plasma concentration cannot be measured directly. The concentration may be assumed to be proportional to and solely dependent on the injected dose:

$$P = ID \cdot k_1, \qquad \text{Eq. 4}$$

where ID is injected dose and k_1 is a constant.

Equations 3 and 4 provide:

$$R(t)/ID = G \cdot k_1 \cdot t. \qquad \text{Eq. 5}$$

Because the left side of the above equation represents fractional renal uptake at time t, Equation 5 implies that the fractional uptake is in proportion to BSA-uncorrected GFR. The basis of Gates' method is the linearity between fractional renal accumulation and BSA-uncorrected GFR, and it appears to be assumed that the plasma concentration early postinjection is determined exclusively by the injected dose.

However, a given injected dose results in various plasma concentrations according to body size, and plasma concentration is considered to be in inverse proportion to the distribution volume. In Gates' method, the plasma concentration is underestimated for patients with small distribution volumes, resulting in overestimation of GFR in small patients. The method should not be used to estimate GFR in children. There seems to be interindividual differences in distribution volume even in adults, although they are smaller than in children. It has been found that adjusting Gates' method for the effect of distribution volume improves its accuracy in adults (*21*).

We chose BSA to represent the distribution volume and assumed that the plasma concentration is in proportion to the injected dose and in inverse proportion to BSA. The following equation holds instead of Equation 4:

$$P = ID \cdot k_2/BSA, \qquad \text{Eq. 6}$$

where k_2 is a constant.

The combination of Equations 3 and 6 yields:

$$R(t)/ID = G/BSA \cdot k_2 \cdot t. \qquad \text{Eq. 7}$$

This equation means that fractional renal uptake at time t is proportional to BSA-corrected GFR. In this study, percent renal

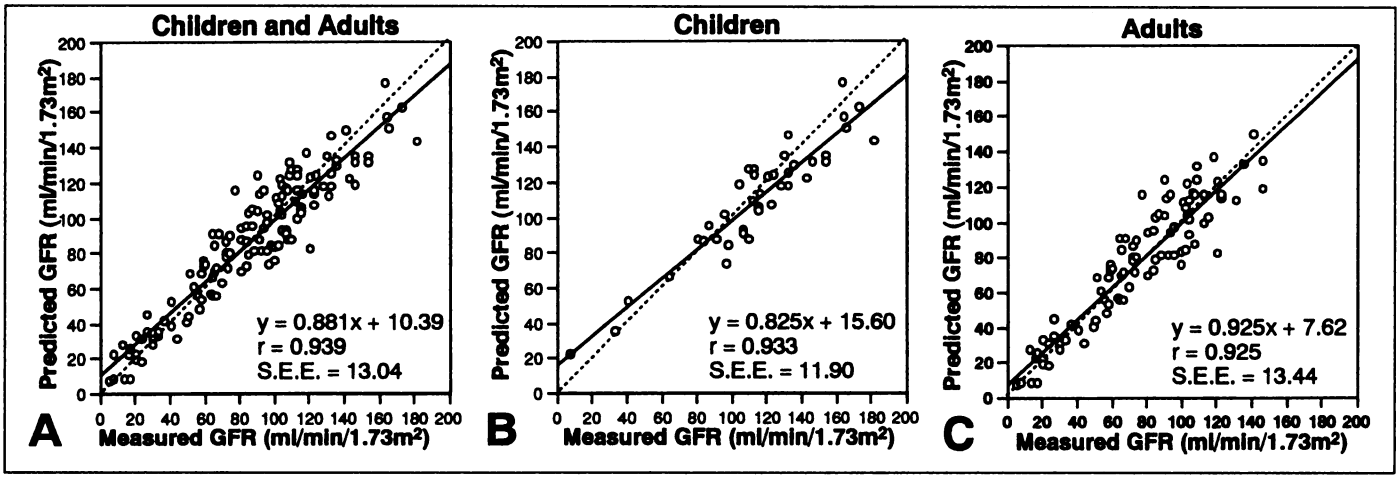

FIGURE 4. Glomerular filtration rate (GFR) predicted by camera-based method presented in this article plotted against GFR measured by reference method. Solid and broken lines represent regression line and line of identity, respectively.

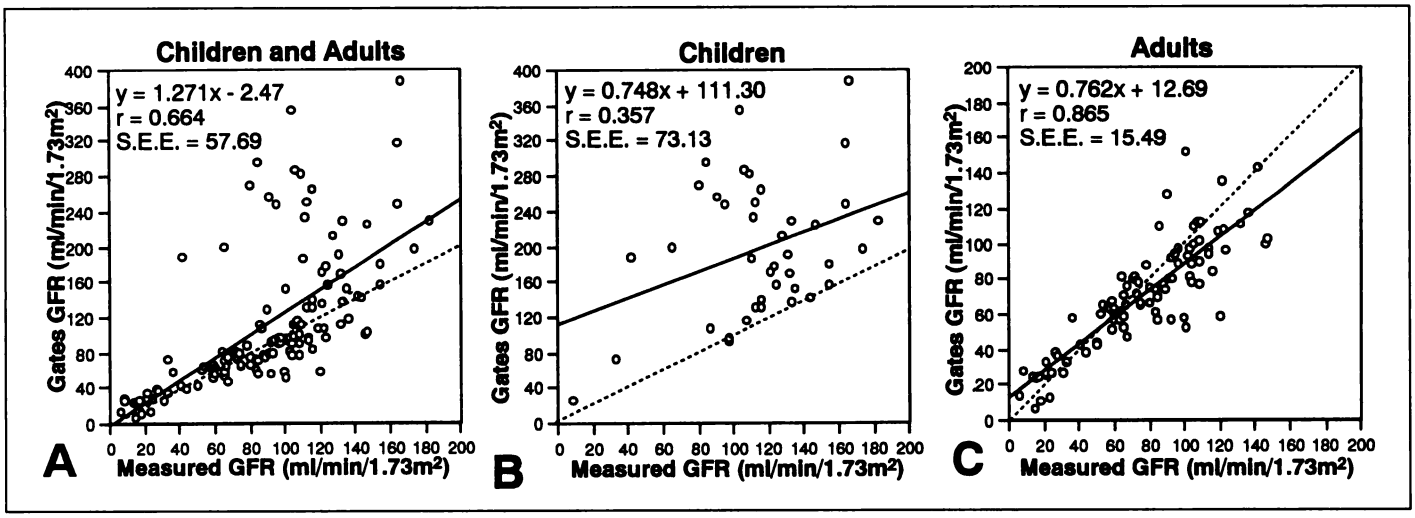

FIGURE 5. Glomerular filtration rate (GFR) calculated by Gates' method plotted against GFR measured by reference method. Solid and broken lines represent regression line and line of identity, respectively.

uptake was closely correlated with BSA-corrected GFR in all patients, including both children and adults, in contrast to poor correlation with BSA-uncorrected GFR. Accurate evaluation of the distribution volume of ^{99m}Tc-DTPA early postinjection is difficult. This result appears to justify the use of BSA as a representative of distribution volume.

We calculated GFR using the regression equation between BSA-corrected GFR and percent renal uptake. This method allowed more precise estimation of GFR in adults than Gates' method, and the accuracy in children was similar to that in adults. The use of the technique presented in this report appears to be acceptable to quantitatively evaluate renal function in both children and adults in routine clinical practice.

The present method gives BSA-corrected GFR directly instead of an estimation of BSA-uncorrected GFR followed by its conversion to a normalized value. GFR is used as an indicator of renal function usually after correction for BSA, especially in pediatric practice, and a technique to directly calculate normalized GFR is preferable to reduce errors in small children with impaired renal function (*22*).

It has been demonstrated that GFR can be predicted on the basis of the relationship between fractional renal uptake and BSA-corrected GFR in children (*7,8*). The results of this study indicate the applicability of the principle irrespective of the patient's age. Shore et al. (*6*) described a method to predict GFR in children using ^{99m}Tc-DTPA renography. Their technique takes into consideration the effect of body size on fractional renal accumulation and was found to provide accurate estimates in children. They, however, commented that their method was unsuccessful in calculating GFR in adults. Body weight was used as an indicator of body size in their technique, whereas BSA was used in this study. This fact may explain, at least in part, the different results between their study and this one. Piepsz et al. (*5*) reported a method to estimate GFR based on the cardiac curve and renal curve after the administration of ^{99m}Tc-DTPA and used it to evaluate renal function in both children and adults. They assessed plasma concentration using the cardiac curve and a blood sample taken at 20 min postinjection, and their technique seems to be more theoretical than ours. However, the cardiac curve is affected by interstitial activity and does not reflect plasma activity accurately. In addition, calibration of the cardiac curve to quantitatively assess the plasma curve is troublesome, requiring blood sampling and conversion of plasma activity measured with a well counter to counts on a gamma camera. Our method appears to offer more convenience and to be better suited to routine use.

There are several technical problems in assessing fractional renal uptake from renal scintigraphy. Counts in the renal ROI should be corrected for background count and soft-tissue attenuation to assess true renal accumulation. In this study, ROIs for the kidneys and background areas were manually drawn, and this procedure may cause interobserver differences. The application of automatic ROI setting to our method remains for future consideration.

An accurate estimate of renal depth is required to correct for soft-tissue attenuation. The equations of Tonnesen et al. (*18*) are popularly used to calculate renal depth (*7,11,13,23*). The formulas were derived from ultrasound measurements obtained from a posterior oblique angle in the sitting position, whereas renal scintigraphy is usually performed in the supine position at present. Calculation using the equations of Tonnesen et al. is found to underestimate renal depth in the supine position in children (*24*) and in adults (*17*). We used the formulas described by Raynaud et al. (*16*) in pediatric patients and those reported by Taylor et al. (*17*) in adult patients. Taylor et al. (*17*) measured renal depth by transmission CT with the patient in the supine position. The formulas of Raynaud et al. were developed using lateral scintigraphy and validated by CT in the supine position (*24*). These equations appear to give more accurate estimates of renal depth compared with the equations of Tonnesen et al. (*18*). The right-to-left difference in renal depth is neglected in the equations of Raynaud et al, (*16*). Although the difference is usually small in children (*24*), ignoring it may cause substantial error in relatively large children. Moreover, the application of different equations to younger children, older children and adults may induce some discontinuity in estimating renal depth in long-term observations. Further sophistication of the method used to calculate renal function may improve the reliability of GFR estimation.

The linear attenuation coefficient for ^{99m}Tc in water is 0.153/cm, and some authors have used this value to correct for soft-tissue attenuation (*7,11,13*). However, the effective attenuation coefficient is lower because of the presence of scattering photons. The reported values of the effective attenuation coefficient range from 0.10 to 0.14/cm (*25–28*). We took the coefficient to be 0.12 on the basis of the reported values.

The injected dose was measured with a gamma camera. Such measurement is often performed without the imaging table

between the syringe and gamma camera. This causes overestimation of the injected dose because the counts in the patient study suffer from table attenuation. This overestimation may be avoided by introducing the attenuation factor of the table (*29*); however, the factor should be determined for each table. We placed the syringe above the gamma camera instead of using correction with an attenuation factor.

It was indicated that renal function in both children and adults can be easily assessed by the method described in this article, although further improvement is desirable as discussed above. Technetium-99m-DTPA was used in this study, and GFR was calculated to represent renal function. Technetium-99m-mercaptotriacetylglycine (MAG3) provides renal scintigrams of better image quality than ^{99m}Tc-DTPA (*30*), and the use of ^{99m}Tc-MAG3 may improve the accuracy of estimating renal function with a gamma camera (*31*). Camera-based methods to obtain renal clearance of ^{99m}Tc-MAG3 have been described for children (*32*) and adults (*29*), and a method applicable to both groups remains to be studied.

CONCLUSION

We demonstrated a high correlation between BSA-corrected GFR and percent renal uptake irrespective of the patient's age. The method presented in this article allows estimation of GFR in both children and adults and may contribute to the quantitative assessment of renal function, especially in nuclear medicine departments to which both pediatric and adult patients are referred.

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