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Abstract

Objective Non-invasive measurement of split renal function is clinically important. Gamma camera-based measurement of glomerular filtration rate (GFR) with ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) is an established method of such measurement; however, it is not as accurate as the plasma sample method. Therefore, study into improving the accuracy of such method is clinically relevant. The aim of the current study was to elucidate the feasibility of gamma camera-based GFR measurement by using renal depth evaluated by lateral scan of ^{99m}Tc-DTPA renography, and comparing the results with those of GFR using renal depth measured by CT, and three representative formulas.

Methods The study population comprised 38 patients (median, 69 years; male 28, female 10; median estimated GFR, 67.4 ml/min) with renourinary disorders. Scintigraphy was performed after intravenous injection of 370 MBq ^{99m}Tc-DTPA by dynamic data acquisition for 20 minutes, followed by a bilateral static scan of the abdomen for 3 minutes. All patients underwent computed tomography (CT) within 2 months from ^{99m}Tc-DTPA renography. GFR was calculated by ^{99m}Tc-DTPA renography using renal depth determined in five ways; lateral scan of ^{99m}Tc-DTPA, CT, and three formulas previously created with using weight, height and age. GFRs were compared with estimated GFR (eGFR). The depth of both kidneys measured as described above was compared and evaluated the laterality of the renal depth.

Results The median values of GFR calculated with renal depth determined by ^{99m}Tc-DTPA renography, CT, and the three formulas were 87.3, 83.9, 67.8, 68.3, and 71.5 ml/min, respectively; and all of them correlated significantly with eGFR (r=0.734, p<2×10-8; r=0.687, p<2×10-7; r=0.728, p<3×10-7; r=0.726, p<3×10-7; and r=0.686, p<3×10-6, respectively). The highest correlation coefficient of the five methods, although no statistical significance was observed.

The depth of both kidneys measured by ^{99m}Tc-DTPA renography was equivalent to that measured by CT, however, those measured by the three formulas were significantly smaller than that measured by ^{99m}Tc-DTPA renography. The depth of the right kidney was larger than that of the left kidney using all three formulas in all patients. However, CT detected only 66% of patients to have a deeper right kidney than left kidney.

Conclusion Lateral sscanning is a feasible procedure for the measurement of renal depth for accurate and reasonable split GFR measurements using ^{99m}Tc-DTPA renography.

Keywords

^{99m}Tc-DTPA renography, Glomerular filtration rate, Split renal function, Renal depth

Introduction

Glomerular filtration rate (GFR) is a standard index of renal function in health and disease. It is measured using urinary clearance of exogenous markers, for example, inulin, iohexol, and iothalamate as non-radioactive materials. Inulin clearance is a standard procedure worldwide, but it is not routinely performed owing to the complexity of the protocol, including timed urine collection and the need for inulin injection. Authentic preparation of inulin was approved for use in 2006 in Japan. Creatinine clearance had until then been used as a physiological estimate of GFR using an endogenous substance[1]. However, creatinine clearance is known to overestimate GFR, especially in patients with renal dysfunction, since serum creatinine concentration is affected by many factors other than glomerular filtration of creatinine [2]. Since GFR is difficult to measure accurately, estimated GFR (eGFR) is widely accepted as a routine index of renal function[3,4].

Measurement procedure of GFR measured using urinary clearance of exogeneous markers are indices of renal function as a whole. Assessment of split renal function is clinically important for patients with unilateral renal disorders, such as renal artery stenosis, urinary obstruction, as well as for healthy kidney donation. The assessment of split renal function has traditionary be performed with radioactive filtration markers. This technique is combined with renal imaging, usually using ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA), and is useful for estimating split renal function by measuring GFR[5,6]. Several procedures to estimate split GFR have been proposed. Measurement of GFR includes methods with or without urine collection and single or multiple blood sampling. The gamma camera-based method is the least invasive method, needing neither urine nor blood samples. Previous studies have shown inaccuracy of this method due to bias or technical factor[6,7].

Although the inaccuracy of gamma camera-based measurement of GFR compared to measurement using the plasma sample method naturally, the camera-based method is more popular than the plasma sample method, since it is non-invasive and convenient for both patients and medical staff. Therefore, improvement in the accuracy of camera-based GFR measurement is clinically relevant. One of the technical reasons for inaccuracy is the attenuation correction for renal accumulation of ^{99m}Tc-DTPA. Attenuation correction is dependent on an accurate estimate of renal depth. A global standard estimate of renal depth may be a formula created by Taylor A (Taylor's formula), which uses weight and height[7]. However, this formula was developed in the United States and may not be suited for Japanese patients. The physical constitution of Japanese people is different from that of the subjects analyzed in the study that Taylor's formula based on[8]. Formulas for renal depth in the Japanese population have been proposed[9–11]. These formulas use weight and height or abdominal thickness to estimate renal depth, and are verified by CT or ultrasonography (US) images.

Direct measurement of renal depth by CT is possible. CT is a common imaging procedure performed to assess both renal anatomy and functional abnormality by using contrast material. However, measurement of renal depth by CT is not slightly realistic, because of patients' inconvenience and radiation exposure. US can be used to measure renal depth; however, the operator's skill and variability are factors that can affect its accuracy.

In the present study, we measured renal depth by lateral scintigraphy with ^{99m}Tc-DTPA to calculate GFR, and compared it with GFR values measured by other methods. Our aim was to test the hypothesis that gamma camera-based measurement of GFR using renal depth measured by lateral scan of ^{99m}Tc-DTPA would be feasible compared with GFR using renal depth measured by CT, two formulas developed in the Japanese population, and Taylor's formula.

Materials and Methods

This study was approved by the institutional review board, and informed consent was obtained from each patient. All patients were informed that the study was performed using ^{99m}Tc-DTPA renography and included a lateral scan by the doctor in charge who suggested the renography. The study was performed between February 2017 and March 2018 in 38 patients (median, 69 years; range 38–83 years, Male 28, Female 10), all of whom underwent CT within 2 months from renography.

The demographic characteristics of the patients are shown in Table 1. Serum creatinine concentration ranged from 0.44 to 2.69 mg/dl, and the median value was 0.86 mg/dl. Estimated GFR ranged from 10.8 to 98.5 mg/dL, with a median value of 67.4 ml/min.

^{99m}Tc-DTPA renography was performed after intravenous injection of 370 MBq ^{99m}Tc-DTPA, with the patient lying in the prone position on the imaging table using a gamma camera (E.CAM, Cannon Co. Ltd., Tokyo Japan) equipped with a parallel hole collimator. Dynamic data acquisition was performed for 20 minutes with a matrix size of 128×128. Data from 2 to 3 minutes after administration were used for calculating GFR by using the dedicated data processing workstation affiliated to the gamma camera.

GFR was calculated by ^{99m}Tc-DTPA renography using renal depth measured in five ways according to Gates' method, as reported previously[12]. Regions of interest (ROIs) were drawn visually over each kidney area on the renal scintigraphy from 2 to 3 minutes. The background ROI was drawn inferolaterally adjacent to each kidney in order to correct the kidney count of ^{99m}Tc-DTPA. GFR was calculated using these data by the Gates' method as follows,

GFR = (right kidney count − background / $e^{-0.153\times\text{right kidney depth}}$) + (left kidney count − background / $e^{-0.153\times\text{left kidney depth}}$) / pre-injection syringe count − post-injection syringe count,

where 0.153 is a linear attenuation coefficient of ^{99m}Tc in the soft tissue.

Measurement of renal depth was performed via ^{99m}Tc-DTPA renography, CT, and three formulas created by Ito T, Ito K, and Taylor A as follows.[8,9,11]

Measurement of renal depth by ^{99m}Tc-DTPA renography

Following routine ^{99m}Tc-DTPA renography, bilateral images of the kidneys with a matrix size of 512×512 were acquired for 3 min. On the lateral images, renal depth was defined as the distance from the middle point of the antero-posterior diameter of each kidney to the body surface on the back (Fig. 1).

Measurement of renal depth by CT

CT was performed with helical scan to cover whole abdominal region in the supine position. Images with 5-mm thick transverse sections at 5-mm intervals were used for the analysis. On axial CT images including the middle point of the long axis of each kidney, the renal depth was defined as the distance from the middle point of the antero-posterior diameter of the kidney to the body surface on the back (Fig. 2).

Measurement of renal depth by Ito T's formula

Depth of the right kidney (RKD) and the left kidney (LKD) was estimated from height and weight as follows[9]:

$RKD = 16.55 \times (Wt/Ht) + 0.66$

$LKD = 17.05 \times (Wt/Ht) + 0.13$

Wt: weight [kg], Ht: height [cm].

Measurement of renal depth by Itoh K's formula

RKD and LKD was estimated from height and weight as follows[11]:

$RKD = 13.6361 \times (Wt/Ht)^{0.6996}$

$LKD = 14.0285 \times (Wt/Ht)^{0.7554}$

Wt: weight [kg], Ht: height [cm].

Measurement of renal depth by Taylor's formula

RKD and LKD was estimated from height, weight, and age as follows[8]:

$RKD = 15.31 \times (Wt/Ht) + 0.022 \times A + 0.077$

$LKD = 16.17 \times (Wt/Ht) + 0.027 \times A - 0.94$

Wt: weight [kg], Ht: height [cm], A: age [year]

Renal depth and laterality of

Depth of both kidneys measured by the five above-described methods were compared and evaluated laterality of the renal depth.

Comparison of GFR

GFR was calculated using renal depth measured by ^{99m}Tc-DTPA lateral scan, CT, and the three formulas. The various GFRs were compared with eGFR as a reference as follows [4],

eGFR (mL/min) = $194 \times \text{Serum creatinine}^{-1.094} \times \text{Age}^{-0.287} \times 0.739$ (if female) $\times$ BSA / 1.73

The Body surface area (BSA) was calculated in Bu Bois method.

Statistical analysis

Association between the calculated GFRs and eGFR were analyzed by correlation analysis. A p-value of <0.05 was considered statistically significant. R (The R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses.

Results

Renal depth was measured in all patient using the five methods. In addition, camera-based measurement of GFR was performed using each of the five renal depth values in all patients. Table 2 summarizes the calculated GFRs. The median GFRs calculated using ^{99m}Tc-DTPA renography, CT, Ito T's formula, Ito K's formula, and Taylor A's formula were 87.3, 83.9, 67.8, 68.3 and 71.5 ml/min, respectively. The median eGFR was 67.4 mL/min. the GFRs calculated with renal depth by each of the three formulas were significantly higher than the eGFR. GFR calculated with renal depth measured by the renography was equivalent to that calculated with renal depth measured by CT.

The relationships between the various calculated GFRs and eGFR are shown in Figure 3. Regression analysis showed significant linear correlations between calculated GFRs and eGFR. The GFRs calculated with renal depth measured by renography, CT, and the three formulas by Ito T, Ito K, and Taylor correlated significantly with eGFR (r=0.734, $p<2\times10^{-8}$; r=0.687, $p<2\times10^{-7}$; r=0.728, $p<3\times10^{-7}$; r=0.726, $p<3\times10^{-7}$; and r=0.686, $p<3\times10^{-6}$, respectively). Among them, the correlation coefficient of GFR calculated with renal depth measured by renography was the highest in these five values, but no statistical significance was found.

The depth of both kidneys measured by ^{99m}Tc-DTPA renography was equivalent to that measured by CT, however, those calculated by the three formulas were significantly smaller than that measured by ^{99m}Tc-DTPA renography (Fig. 4). The depth of the right kidney was found to be larger than the left kidney in all patients when each of the three formulas were used. In contrast, deeper right kidneys were only found in 65.8% (25/38) of the patients when CT was used.

Discussion

The present study showed that GFR calculated using renal depth measured by ^{99m}Tc-

DTPA renography was closest to eGFR, and had a stronger correlation with eGFR than CT and the three formulas by Ito T, Ito K, and Taylor, although no statistical significance was observed. The depth of both kidneys measured by ^{99m}Tc-DTPA renography was equivalent to that measured by CT, however, those measured by the three formulas were significantly smaller than that measured by ^{99m}Tc-DTPA renography.

Although Taylor's formula is a standard method that is used worldwide to calculate renal depth, the renal depth by Taylor's formula may be different from the true value result in inaccurate GFR calculations. One of the reasons for the difference we had supposed was that the physical constitution of Japanese people was different from that of people in the United States. We had also supposed that Itoh T's and Ito K's formulas were more accurate than Taylor's formula when used for ^{99m}Tc-DTPA renography in the Japanese population; however, they are not closest to eGFR nor the best correlation with eGFR in the present study.

Calculation of renal depth by the three formulas with height, weight, and/or age examined in the present study is easy to be done; however, there are some disadvantages that should be considered when they are used for GFR measurement by renography. The depth of the right kidney was always calculated to be larger than that of the left kidney when all three formulas were used, which is not realistic. For example, when the height, weight, and age are assumed with the medians of patients in the present study (163 cm, 63 kg, and 69 years-old, respectively), the respective depths of the right and left kidneys were: 7.06 cm and 6.72 cm with Ito T's formula; 7.01 cm and 6.84 cm with Ito K's formula and 7.51 cm and 7.17 cm with Taylor's formula. In the clinical setting, patients do not always have a deeper right kidney than the left, because many patients that undergo renography have unilateral renourinary disease, such as obstructive uropathy, renal artery diseases, pyelonephritis, congenital anomaly, tumor, and cystic diseases. Moreover, in the present study, the percentages of patients with deeper right kidney measured using CT and renography were 65.8% (25/38) and 39% (15/38), respectively. The difference in renal depth laterality between CT and renography may be due to the position of the patient when undergoing said procedures; i.e., CT was performed with the patient in the supine position, and renography was performed with the patient in the prone position. Regardless, the direct measurement of renal depth is necessary to evaluate split renal function while considering the individual difference in the laterality of the renal depth.

Accurate estimation of the split renal function is indispensable for pretherapeutic assessment, post-therapeutic estimation of the residual renal function, and also for kidney donation.

In the present study, GFR calculated with renal depth measured by the renography was not less accurate than that calculated with renal depth measured by CT , when compared with eGFR, although no statistical significance was observed. These results suggest that measurement of renal depth with ^{99m}Tc-DTPA renography is suitable for calculating GFR by the camera-based method. Simultaneous measurement of bilateral renal depth and renal function is rational, as the renal positions may be different by the patient's position. Other merits of renal depth measured by ^{99m}Tc-DTPA renography are that there is no unnecessary exposure to radiation, and that it is less costly to the patient, in terms of both time and money, because CT would be unnecessary.

In the current study, ^{99m}Tc-DTPA renography was performed with the patient lying in the prone position. Renal scintigraphy can be performed with the patient in the supine position, with the gamma camera underneath the imaging table. However, gamma radiation would be attenuated by the table if this approach is used, resulting in the inaccuracy of quantitation. The attenuation of gamma radiation by the imaging table could be corrected by using an appropriate attenuation coefficient. However, accurate correction is not easily done, and could potentially be another source of inaccuracy. Therefore, GFRs calculated with the patient in the prone position, as was performed in the current study, would be more accurate as compared with that performed with the patient in the supine position.

The standard estimate of split GFR is a gamma camera method using ^{99m}Tc-DTPA renography[13,14]. However, other modalities have been used to measure GFR as well. Single-kidney GFR has been measured by using multidetector CT[15–18] . In studies by You et al. and Yuan et al., GFR clculated by contrast enhansment CT measurement shows significant correlation, although underestimated and overestimated respectively, with gamma-camera method of GFR measurement as a reference[15,16]. Kwon et al. reported that GFR measured by CT is associated with iothalamate clearance for single kidney[18]. However, the authors pointed out that CT-measured GFR is limited by the need for contrast media and by the radiation burden, which should be considered carefully for the safety of individual patients and considered in patients undergoing CT for clinical benefit.

Because the effective dose incurred in the studies that Kwon et al. reported (26–27 mSv) is much higher than that associated with typical CT examinations. Another demerit of CT measurement is that contrast material must be used for patients with renal dysfunction.

A comparative study between iohexol CT and ^{99m}Tc-DTPA renography reported that the correlation coefficient between the two methods was 0.98, and the authors concluded that due to the higher radiation dose from CT than from ^{99m}Tc-DTPA injection, relative GFR determination with CT should be performed when there is also a diagnostic need to reveal the morphology[19].

Currently, dynamic contrast-enhanced MRI (DCE-MRI) is being investigated for measurement of GFR. Many protocols based on the intrarenal kinetics of contrast materials have been proposed for estimating GFR by DCE-MRI; however, the accuracy of this method has not been verified by the standard reference, DCE-MRI based measurements need consolidation before introduction into clinical practice[20–25]. Wan-Li Z et al. reported comparative results of DCE-MRI- and ^{99m}Tc-DTPA-based measurements of allograft renal function. DCE-MRI based measurements showed significant correlation with ^{99m}Tc-DTPA method as a reference standard[25]. However, to the best of our knowledge, there has been no study comparing the use of MRI and ^{99m}Tc-DTPA for orthotopic kidneys. A disadvantage of the DCE-MRI method is that the use of gadolinium-containing contrast agents has been identified as a trigger for the development of nephrogenic systemic fibrosis in patients with advanced renal diseases.

Since gamma camera renography is a standard procedure to evaluate split renal function, refinement of the study method and improvement of accuracy are important for the assessment of new methods to calculate split renal function, as shown above.

The current study has several limitations. First, although eGFR is a standard estimate in many hospitals, it is just an estimate value, and is not suitable for a reference standard of GFR. The present study did not assess the absolute value of GFR, nor the value of creatinine clearance. In addition, individual laterality and variability of renal depth according to body position were not validated, because reference standards of laterality and postural difference of bilateral renal depth were not available. Additionally, although ^{99m}Tc-DTPA renography was performed with the patient lying in the prone position in order to secure the accuracy of the measurement by excluding the need for attenuation correction by the imaging table, the supine position is common in routine renography.

Finally, the sample size of the current study was relatively small, and the underlying diseases are variable in patients studied.

Conclusion

Lateral scan is a more feasible procedure for measure renal depth for accurate camera-based GFR measurement using ^{99m}Tc-DTPA renography in the Japanese population than CT and the standard formulas.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All the procedures in the present studies involving human participants were performed in accordance with the ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by our institutional review board at Fukushima Medical University.

Informed consent Informed consent was obtained from all participants included in the study

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Table 1 Baseline clinical characteristics of patients

Characteristics	Median (range, min.–max.)
Age (year)	69 (38–83)
Height (cm)	163.3 (138.4–177.0)
Weight (kg)	63.9 (37.6–83.5)
Serum creatinine level (mg/dl)	0.86 (0.44–2.69)
Estimated GFR (ml/min)	67.4 (10.8–-98.5)

Table 2 Comparison between GFR using renal depth measured by ^{99m}Tc-DTPA renography (Renography), CT, and three formulas created by Ito T, Ito K, and Taylor

Method	Median GFR (range, min. –max.)
Renography	87.3 (11.5–170.5)
CT	83.9 (10.1–148.0)
Ito T's formula	67.8 (-0.2–130)
Ito K's formula	68.3 (0.1–133.5)
Taylor's formula	71.5 (0.6–126.2)

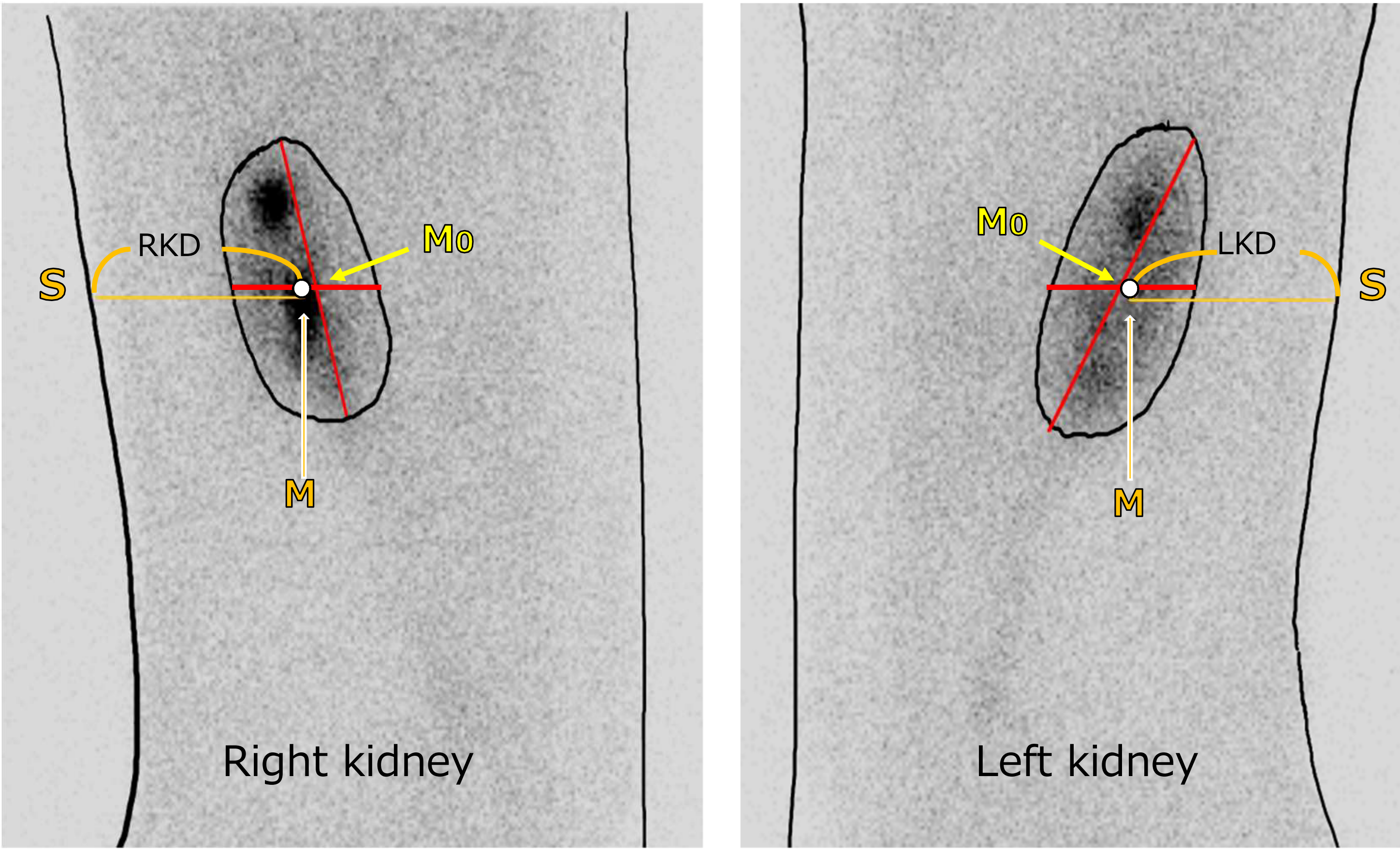


Figure 1

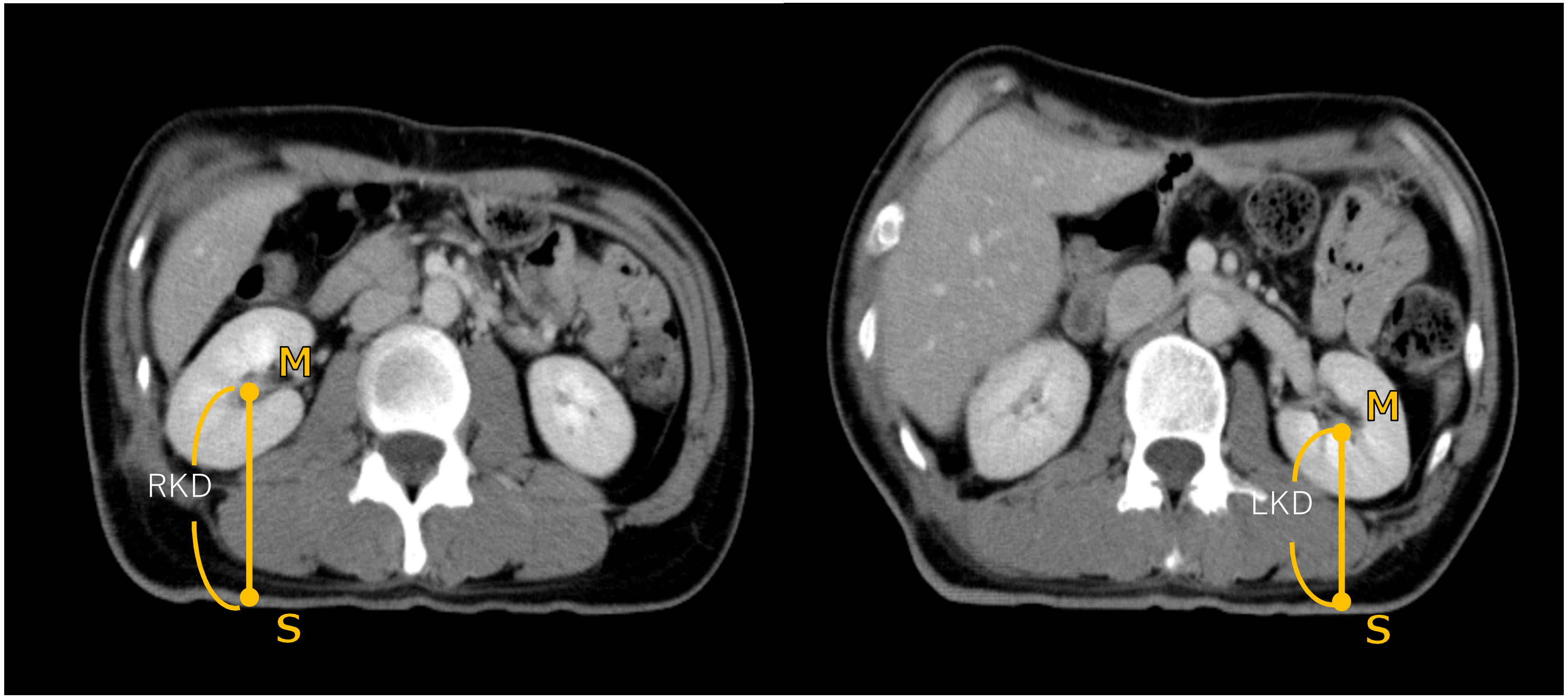
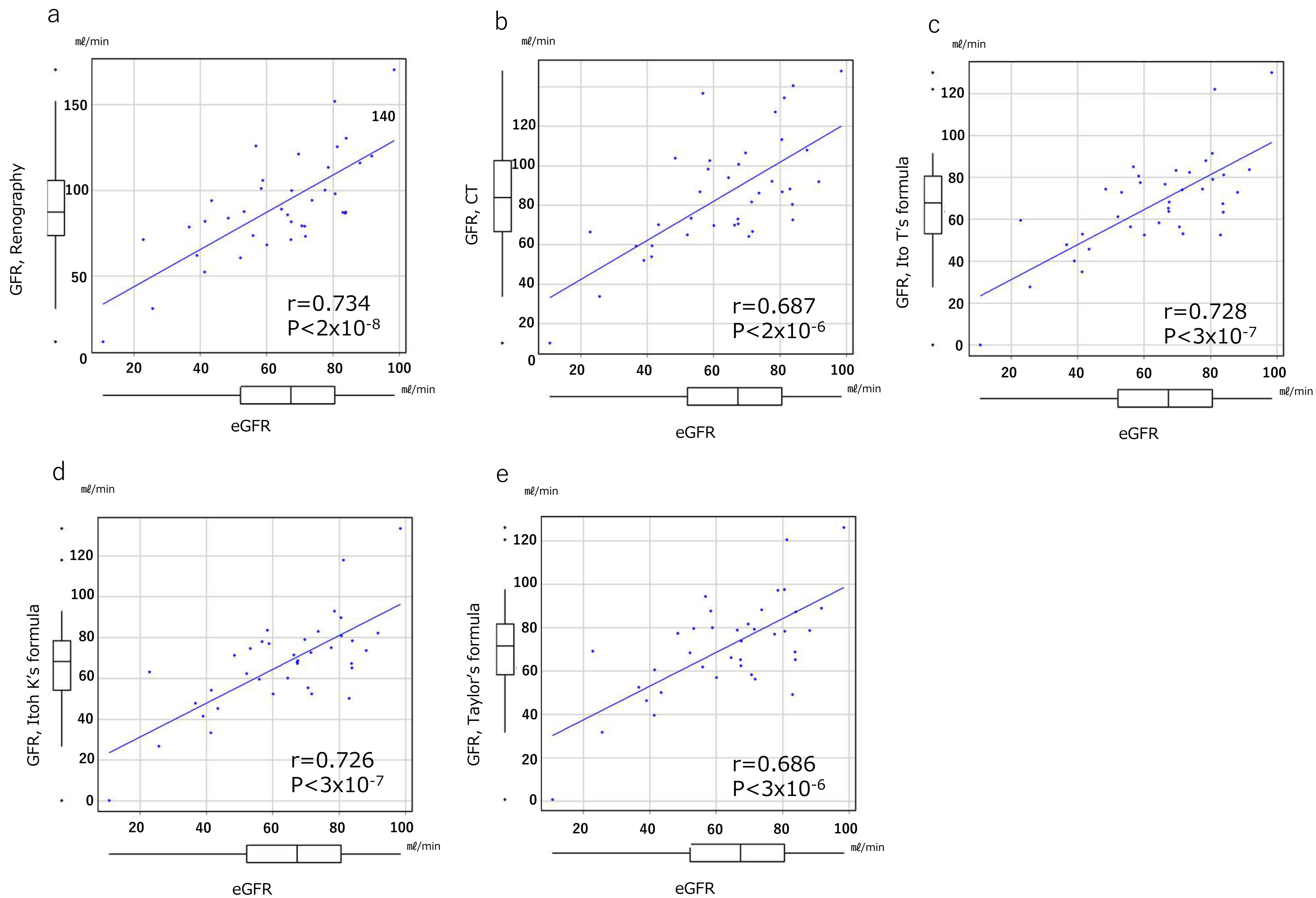


Figure 2



a
mℓ/min
GFR, Renography
150
100
50
0
140
20
40
60
80
100
mℓ/min
eGFR
r=0.734
P<2x10-8
b
mℓ/min
GFR, CT
120
100
80
60
40
20
0
20
40
60
80
100
mℓ/min
eGFR
r=0.687
P<2x10-6
c
mℓ/min
GFR, Ito T's formula
120
100
80
60
40
20
0
20
40
60
80
100
mℓ/min
eGFR
r=0.728
P<3x10-7
d
mℓ/min
GFR, Itoh K's formula
120
100
80
60
40
20
0
20
40
60
80
100
mℓ/min
eGFR
r=0.726
P<3x10-7
e
mℓ/min
GFR, Taylor's formula
120
100
80
60
40
20
0
20
40
60
80
100
mℓ/min
eGFR
r=0.686
P<3x10-6

Figure 3

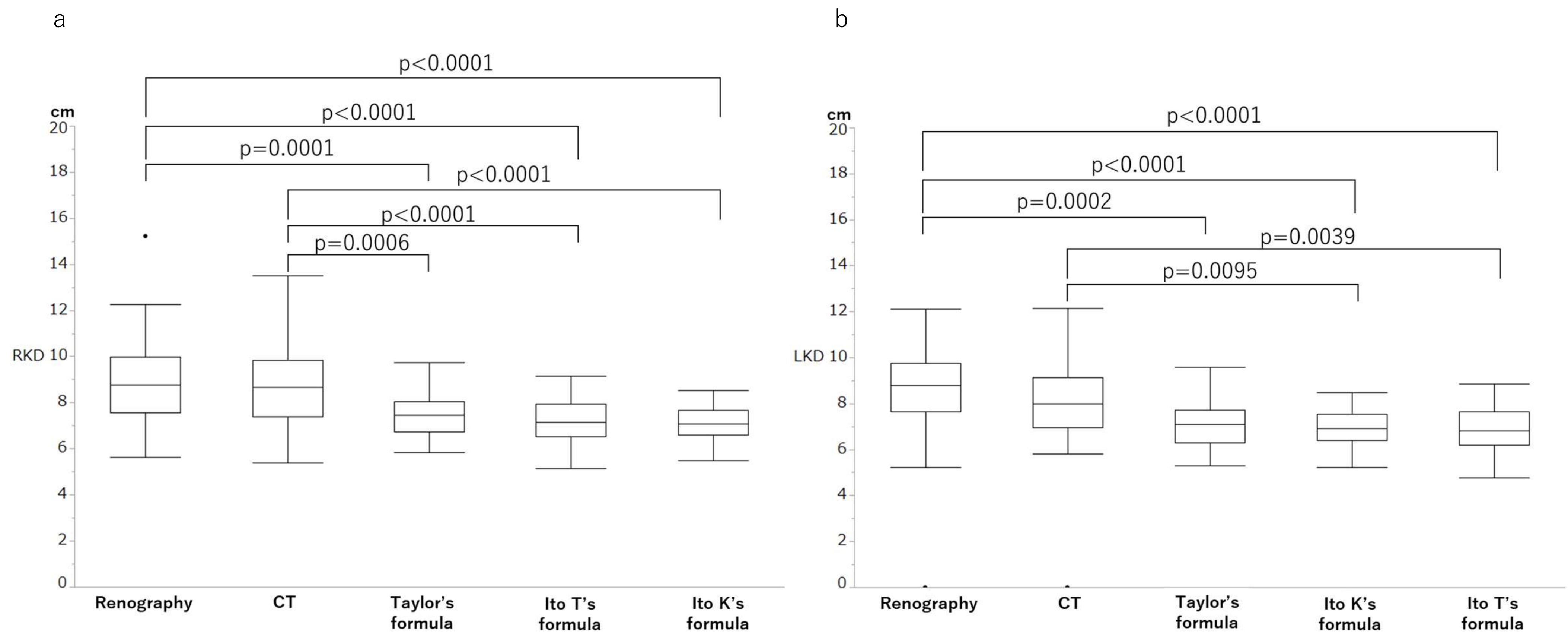

a
p<0.0001
p<0.0001
p=0.0001
p<0.0001
p<0.0001
p=0.0006
cm
RKD
20
18
16
14
12
10
8
6
4
2
0
Renography
CT
Taylor's formula
Ito T's formula
Ito K's formula
b
p<0.0001
p<0.0001
p=0.0002
p=0.0039
p=0.0095
cm
LKD
20
18
16
14
12
10
8
6
4
2
0
Renography
CT
Taylor's formula
Ito K's formula
Ito T's formula

Figure 4

Figure Legends

Fig. 1 Measurement of renal depth by ^{99m}Tc-DTPA renography

Measure the maximum length of the kidney on the lateral image to decide the middle point M0. Then draw a line going through point M0 and perpendicular to the gamma camera. Measure the antero-posterior diameter of the kidney on the line, and the middle point of the diameter is defined as M. The distance from point M to the body surface on the back (S) is defined as the depth of the kidney.

RKD, right kidney depth; LKD, left kidney depth

Fig. 2 Measurement of renal depth by CT

Two axial CT slices including the middle point of the long axis of the right and left kidneys are chosen. Then find the middle point (M) of the antero-posterior diameter of the kidney on each image. The distance from point M to the body surface on the back (S) is defined as the depth of the kidney.

RKD, right kidney depth; LKD, left kidney depth

Fig. 3 The relationships between eGFR and GFRs calculated using renal depth measured by five different methods.

a GFR calculated using the renal depth measured by ^{99m}Tc-DTPA renography

b GFR calculated using the renal depth measured by CT

c GFR calculated using the renal depth measured by Ito T's formula

d GFR calculated using the renal depth measured by Ito K's formula

e GFR calculated using the renal depth measured by Taylor's formula.

Fig. 4 Comparison of the depth of both kidneys measured by the five methods. p-values are indicated only when $p<0.05$. No statistical significance is noted unless otherwise indicated.

a Depth of the right kidney measured by the five methods

b Depth of the left kidney measured by the five methods