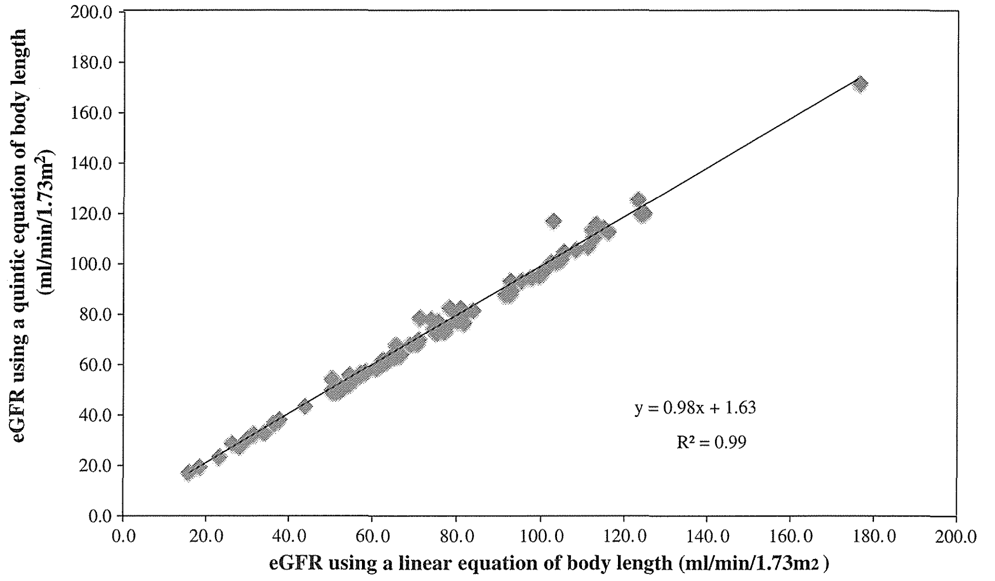

Fig. 3 Analysis of two eGFR equations in pediatric CKD patients aged between 2 and 11 years old. The two equations are eGFR using a linear and quintic equation of body length, respectively. The regression equation was $y = 0.976x + 1.63$. A significant positive correlation was observed in children with CKD aged between 2 and 11 years old, with a correlation coefficient of 0.995

Table 2 Performance of GFR-estimating equations in all 131 subjects

Variable and equation	All (n = 131)	Aged <12 years (n = 76)	Aged ≥12 years (n = 55)
Bias (ml/min/1.73 m^2)			
New polynomial formula	13.4 ± 10.7	12.9 ± 10.4	14.2 ± 11.1
Simple linear formula	14.4 ± 11.6***	13.3 ± 10.5***	15.8 ± 12.9***
Original Schwartz's formula	17.4 ± 13.2***	14.4 ± 11.1***	21.6 ± 14.8***
Updated Schwartz's formula	15.5 ± 15.5***	15.8 ± 15.3***	14.9 ± 11.2***
P_{30} (%)			
New polynomial formula	84 (77–90)	84 (74–92)	84 (76–90)
Simple linear formula	82 (75–89)^{ns}	83 (73–91)^{ns}	82 (74–89)^{ns}
Original Schwartz's formula	60 (51–68)***	67 (55–77)*	60 (51–69)***
Updated Schwartz's formula	69 (61–77)**	66 (54–76)**	69 (60–77)^{ns}
Root mean square error (ml/min/1.73 m^2)			
New polynomial formula	17.3	16.7	18.2
Simple linear formula	18.1	17.1	18.5
Original Schwartz's formula	17.6	16.2	16.5
Updated Schwartz's formula	18.1	17.1	18.5

Bias is the absolute value of mGFR minus eGFR and is reported as mean ± standard deviation; P_{30} refers to percentage of GFR estimates that are within 30 % of the mGFR, with 95 % confidence intervals given in parentheses

The new polynomial formula is the following equations: eGFR = 110.2 × (reference serum Cr/patient's serum Cr) + 2.93, and reference serum Cr levels (y) are shown by the following two equations of body length (x (m)): males: $y = -1.259x^5 + 7.815x^4 - 18.57x^3 + 21.39x^2 - 11.71x + 2.628$, and females: $y = -4.536x^5 + 27.16x^4 - 63.47x^3 + 72.43x^2 - 40.06x + 8.778$

The simple linear formula is the following equation: eGFR = 0.35 × body length (cm)/serum Cr level (mg/dl)

The original Schwartz's formula is the following equations: eGFR = k × body length (cm)/serum Cr level (mg/dl). The coefficient k is 0.55 in children 2–12 years old and 0.55 and 0.70 in females and males over 12 years old, respectively

The updated Schwartz's formula is the following equations: eGFR = 0.413 × body length (cm)/serum Cr level (mg/dl)

eGFR estimated glomerular filtration rate, *mGFR* glomerular filtration rate measured by the inulin clearance method

ns Not significant; * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ show the statistical significance of the difference from our new formula

We reported that the new bedside Schwartz formula cannot be used when estimating GFR in Japanese children, especially between 1 and 16 years old, including the adolescent period, for reference serum Cr levels of our 1,074 subjects [6], showing a gradual significant decrease of eGFR with age [16]. There seems to be a large problem in that the ranges of the reference value for boys >12 years old and girls >14 years old overlap with the range for CKD

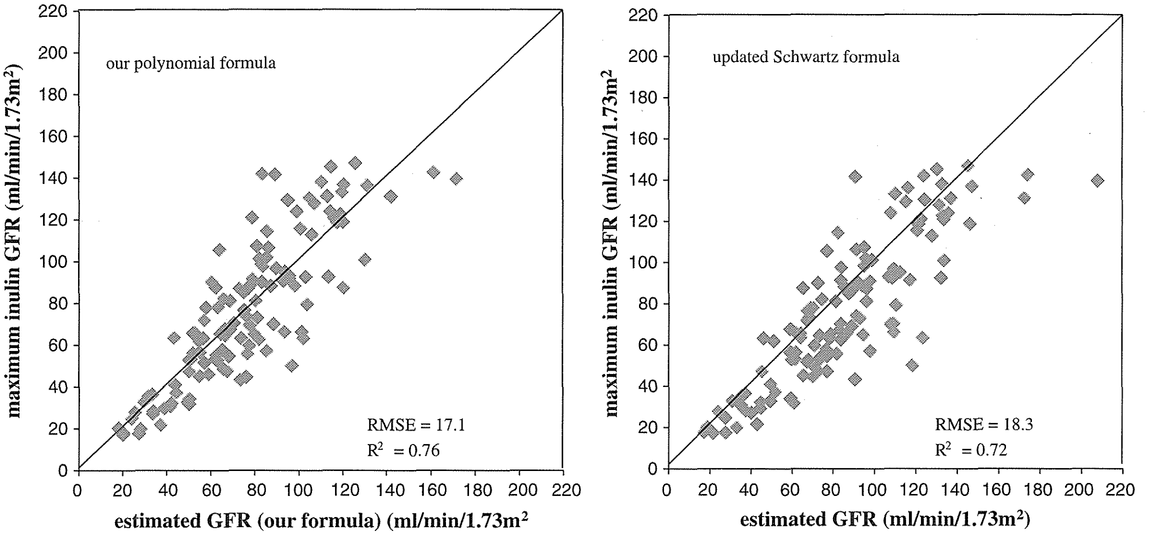

Fig. 4 Correlation between the estimated and measured maximum inulin GFR in CKD patients aged between 2 and 16 years old. *Left* Measured maximum inulin GFR versus the estimated GFR obtained using our polynomial formula. *Right* Measured maximum inulin GFR versus estimated GFR obtained using the updated Schwartz formula. *Smoothed lines* show the fit of the data

stage 2. Our results indicated that the eGFR value derived by the new bedside Schwartz formula decreased gradually with age in children with normal renal function. We doubt that the new "bedside" Schwartz formula cannot be used to estimate the GFR in Japanese pediatric CKD patients as well as in children with normal renal function.

When we performed the nationwide, population-based survey of children with pre-dialysis CKD in Japan, we used the new diagnostic criteria for CKD in children [17]. Then stage 3–5 CKD was classified as serum Cr more than twice, four times, and eight times the median reference serum Cr levels matched for age and sex, which were previously determined in Japanese children [6]. However, with those diagnostic criteria, we were not able to determine the numerical eGFR in a CKD patient. In a similar way of thinking, Pottel et al. [18] reported the simple height-independent eGFR equation in children.

At any rate, the new bedside Schwartz formula has an inherent problem in that it uses the same coefficient between the ages of 1 and 16 years old. In addition, we assumed that renal function and muscle mass show ethnic differences. Therefore, it is necessary to establish a specialized estimated GFR equation for use in Japanese children and adolescents.

We developed an estimated GFR equation for use in Japanese children aged between 2 and 11 years old whose reference serum creatinine levels were thought to be proportional to body length as follows: eGFR (ml/min/1.73 m^2) $= 0.35 \times$ body length (cm)/serum Cr level (mg/dl) [8]. In the present study, we presented the complex estimated GFR equation using polynomial formulae for reference serum creatinine levels with body length in Japanese children aged between 2 and 18 years old, i.e., all children and adolescents except infants.

Our polynomial formula had lower bias ($P < 0.001$) than our simple linear formula [8] as well as the original [1–4] and updated [5] Schwartz's formula in all 131 subjects and each age category, such as <12 and ≥12 years old. In addition, the % accuracy of our polynomial formula was superior to the original and updated Schwartz's formula ($P < 0.001$ and $P < 0.01$, respectively). Ultimately, our new formula derived from the body length and serum Cr in Japanese children aged between 2 and 18 years old will be useful for estimating their renal function despite the complicated formula as computerization of medical care simplifies their application. Although the polynominal eGFR equation seems complex, we use the quintic equation to estimate the GFR of children of all ages except infants by one expression. Especially the equation will be useful because we were able to use it even in adolescents. Limitations of our study include the small number of subjects, especially females, and having no other data set to validate the equations. Actually, the prevalence of pre-dialysis stage 3–5 CKD was about 3 cases/100000 Japanese children, which was lower than that reported in the ItalKid [19] and REPIR II Projects [20], and the number of Japanese children with stage 3–5CKD was estimated to be about 500 [17]. Therefore, further studies are required to validate our equations using a different data set. However, we consider that the new polynomial eGFR formula showing the relationship with the body length and serum Cr level may be applicable for clinical screening of renal function in Japanese children and adolescents aged between 2 and 18 years, and these methods of evaluation of renal function in children will be useful worldwide.

Acknowledgments This study was financially supported by the Kidney Foundation, Japan, which enabled us to examine blood and urine specimens gathered throughout Japan. We thank Takeshi Matsuyama, MD, Yohei Ikezumi, MD, Midori Awazu, MD, Takashi Sekine, MD, Mayumi Sako, MD, Takuji Yamada, MD, Yuko Akioka, MD, Hirotsugu Kitayama, MD, Masataka Hisano, MD, and Kazumoto Iijima, MD, of the Committee of Measures for Pediatric CKD, for their contributions to the improvement of this manuscript, and Kenichi Satomura, MD, and Yuhei Ito, MD, for their contributions to the participation of patients in this study.

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ORIGINAL ARTICLE

Cystatin C-based equation for estimating glomerular filtration rate in Japanese children and adolescents

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Abstract

Background Renal inulin clearance is the gold standard for evaluation of kidney function, but is compromised by problems of collecting urine samples in children, especially those <6 years or with a bladder dysfunction. Therefore, we should utilize the serum cystatin C (cysC)-based estimated glomerular filtration rate (eGFR) for measuring serum cysC. The purpose of the present study is to determine the applicability of the new serum cysC-based eGFR in Japanese children and adolescents, including infants with chronic kidney disease (CKD), for evaluation of renal function.

Methods Inulin clearance and standardized serum cysC level determined by the colloidal gold immunoassay were measured in 135 pediatric CKD patients between the ages of 1 month and 18 years with no underlying disease that affects renal function except CKD, to determine serum cysC-based eGFR in Japanese children and adolescents.

Results We showed the inulin clearance by expression of 1/serum cysC in pediatric CKD patients, which resulted in the equation: inulin GFR (mL/min/1.73 m^2) = 104.1 × 1/serum cysC (mg/L) − 7.80. We also validated the cysC-based eGFR formula for Japanese adults. eGFR values obtained with the adult formula significantly underestimated GFR by approximately 8 % in children with CKD.

Conclusion We determined the new cysC-based eGFR formula is useful for clinical screening of renal function in Japanese children and adolescents, including infants.

Keywords Estimated glomerular filtration rate · Japanese children · Cystatin C-based equation · Chronic kidney disease

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Introduction

A single measurement of the serum concentration of cystatin C (cysC), a 13-kDa non-glycosylated low-molecular-weight protein [1] and a proteinase inhibitor involved in the intracellular catabolism of proteins [2], has commonly been used to determine kidney function. CysC is produced at a constant rate in the body, freely filtered by the glomeruli, not secreted or reabsorbed by kidney tubules, and is excreted mainly by the kidneys.

Glomerular filtration rate (GFR) is universally used as a measure of kidney function. Renal inulin clearance to measure GFR directly is compromised by problems of collecting urine samples in children, and therefore the estimated GFR (eGFR) should be utilized in such cases. We developed a serum creatinine (Cr)-based eGFR equation for use in children aged between 2 and 11 years as follows—eGFR (mL/min/1.73 m^2) = 0.35 × body length (cm)/serum Cr level (mg/dL) [3], and complex eGFR equations using polynomial formulas for reference serum Cr levels with body length in Japanese children aged between 2 and 18 years, i.e., all children and adolescents except infants [4]. However, we use reference serum Cr levels with body length in the formulas and GFR varies to some extent among children, increasing from approximately 30−100 % of the level in adults during the 2 years

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after birth. Therefore, the serum Cr-based formulas cannot be used in children under 2 years. Here, we present the serum cysC-based eGFR equation for use in all children and adolescents, including infants, in Japan.

Materials and methods

Study population

A total of 174 children (113 males and 61 females) between the ages of 1 month and 18 years with chronic kidney disease (CKD) presenting at the facilities of the members for the Committee of Measures for Pediatric Chronic Kidney Disease between 2008 and 2011 were included in this study. Excluding the cases described below, a total of 135 cases (88 males and 47 females) were included in formulating the new eGFR. The study was approved by the local ethics boards of each institution, and written informed consent was obtained from the parents of each child. The ethics committee approval number in Aichi Children's Health and Medical Center is 200810.

GFR and serum cysC measurements

Data regarding serum cysC values and renal inulin clearance (Cin) measured at the same time were reviewed.

The GFR was measured with inulin [5, 6] and adjusted to body surface area and was standardized to 1.73 m^2. Cin was measured from samples taken twice over 2 h under fasting and hydrated conditions by the continuous infusion method (Fig. 1), which was performed as reported previously [3, 4]. To calculate inulin loss, GFR was estimated from serum Cr by the Schwartz formula [7–10]. Therefore, the patients received an inulin load of 0.7 × eGFR mL/m^2/h with calculation of the body surface area by the Haycock method [11].

The standardized method of cysC measurement traceable to ERM-DA471/IFCC became available in 2011. A project team for verification of immunoassay standardization for serum cysC from the Japan Society of Clinical Chemistry, including investigators from 15 manufacturers, analyzed the performance of the 15 serum cysC immunoassays available in Japan. Transfer factors from ERM-DA471/IFCC to calibrators of the participating immunoassays were obtained. Standardization was achieved among most of the assays. Further improvement and development were needed for precision and accuracy in the performance of a few immunoassays [12]. The colloidal gold immunoassay (Alfresa Pharma Corporation, Osaka, Japan) is one of the immunoassays in which standardization was achieved, and the correction factor is 0.96 using the regression model. In the present study, serum cysC values of 174 samples were measured by the colloidal gold immunoassay before 2011, and calibrated to the standardized value using this correction factor, similar to the method of Horio et al. [13].

Serum samples were stored at −70 °C until serum cysC was measured by SRL Inc. (Tokyo, Japan). The serum cysC level was determined using a cysC assay (Nescaute GC cystatin C; Alfresa Pharma Corporation) on a Bio-Majesty JCA-BM8020 (JEOL Ltd., Tokyo, Japan). Urine and serum samples were stored at 4 °C until urine and serum inulin were measured by SRL Inc. The urine and serum levels of inulin were determined by an enzymatic method using an automated analyzer (Hitachi 7170; Hitachi Ltd., Tokyo, Japan) with Dia-color-inulin (Toyobo Co., Ltd., Tokyo, Japan).

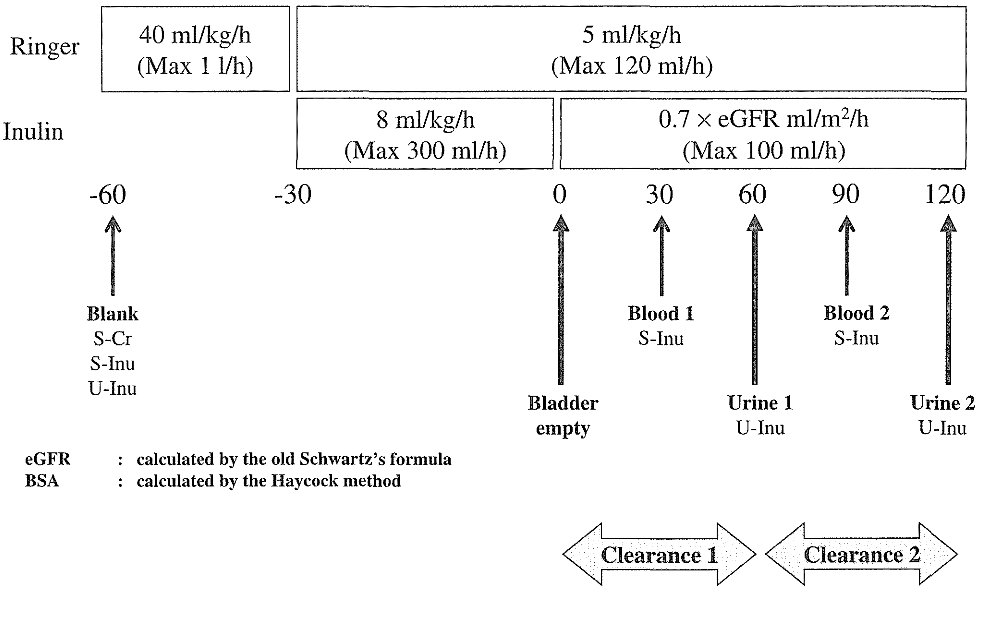

Fig. 1 Inulin clearance method standardized according to the Committee of Measures for Pediatric CKD. Inulin was given intravenously to achieve extracellular fluid levels of 20 mg/dL in testing. For this purpose, the rates of inulin infusion must equal the rates of loss in the urine, which were calculated using the Schwartz formulas based on serum Cr level

Examination for the appropriateness of the correction factor

Serum cysC values of 86 frozen samples of 174 children were measured by colloidal gold immunoassay, which was traceable to ERM-DA471/IFCC in 2012. We compared the standardized values using the correction factor to the values obtained by this standardized method in these 86 cases.

eGFR based on serum cysC

The equation for eGFR was determined using univariate linear regression. The dependent variable is measured GFR, and the independent variable is 1/cysC.

Exclusion criteria and cases that were excluded

The exclusion criteria in this study were (a) severe obstructive uropathy, (b) infection during treatment, (c) inflammatory disease, (d) dehydration, (e) myopathy, (f) severe cardiac, hepatic, or pancreatic disease, (g) pregnancy or the possibility of pregnancy, (h) nursing, and (i) refusal or inability to give informed consent. Two cases with myopathy were excluded because of violation of the protocol. In this study, doses of intravenous inulin administration were decided as blood concentrations were constant during testing by calculating the eGFR by the Schwartz formula. Therefore, cases in which the ratios of urine inulin excretion and intravenous inulin administration were <0.5 or >1.5 were excluded from this study, because there may have been failure to collect all urine. As we were interested in determining eGFR of cases with GFR <120 mL/min/1.73 m^2, we excluded cases with GFR >150 mL/min/1.73 m^2 to increase reliability.

Application of the serum cysC-based eGFR formulas for Japanese adults to our materials

Horio et al. [13] reported the serum cysC-based eGFR formulas in Japanese adults—$\text{eGFR} = (104 \times \text{cysC}^{-1.019} \times 0.996^{\text{age}}) - 8$ in males and $(104 \times \text{cysC}^{-1.019} \times 0.996^{\text{age}} \times 0.929) - 8$ in females. It is desirable that the same estimation equations can be used in both children and adults. Therefore, we compared the values obtained with application of Horio's formula for adults to pediatric CKD patients with their Cin values.

Statistical analyses

All analyses were conducted using Microsoft Excel 2010 and the JMP 8 statistical software package (SAS Institute

Table 1 Characteristics of 135 children included in this study

Characteristics	Median (IQR)	*n*
Total		135
Age (years)	10.6 (7.0–13.7)	
<6 years		21
≥6 and <12 years		60
≥12 years		54
Gender		
Male		88
Female		47
Renal abnormality		
Congenital anomalies of the kidney and urinary tract		57
Reflux nephropathy		16
Idiopathic nephrotic syndrome		13
Renal transplant		7
Chronic glomerulonephritis		5
Nephronophthisis		5
Neurogenic bladder		4
Polycystic kidney disease		3
Alport's syndrome		3
Miscellaneous		22
Height (cm)	133.4 (111.4–151.1)	
<6 years	94.4 (84.5–101.7)	
≥6 and <12 years	123.5 (110.6–132.0)	
≥12 years	153.4 (145.4–162.8)	
Weight (kg)	29.2 (18.9–41.6)	
<6 years	13.6 (11.7–16.4)	
≥6 and <12 years	23.2 (18.8–28.9)	
≥12 years	46.5 (37.9–50.7)	
Body surface area (m^2)	1.03 (0.77–1.30)	
<6 years	0.60 (0.53–0.67)	
≥6 and <12 years	0.89 (0.76–1.03)	
≥12 years	1.41 (1.23–1.51)	
Serum cystatin C (mg/dL)	1.29 (0.99–1.61)	
<6 years	1.42 (1.08–1.67)	
≥6 and <12 years	1.21 (0.97–1.51)	
≥12 years	1.29 (0.99–1.57)	
Average inulin GFR (mL/min/1.73 m^2)	66.3 (46.1–93.3)	
<6 years	51.4 (33.1–73.0)	
≥6 and <12 years	68.3 (50.0–95.5)	
≥12 years	69.2 (52.4–91.9)	
Maximum inulin GFR (mL/min/1.73 m^2)	71.0 (52.9–97.2)	
<6 years	55.3 (34.1–74.4)	
≥6 and <12 years	77.9 (55.5–106.5)	
≥12 years	76.2 (53.9–93.6)	

IQR interquartile range

Inc, Cary, NC, USA). Linear regression analyses were performed to evaluate relationships between the ratios of 1/serum cysC and Cin. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Results

Characteristics of the study population

Of the 174 children studied, 2 cases with violation of protocol, 32 cases with ratios of urine inulin excretion and intravenous inulin administration <0.5 or >1.5, and 5 cases with GFR >150 mL/min/1.73 m^2 were excluded from this study. Therefore, a total of 135 cases (88 males; 65 %) were included in the study (Table 1); 42 % had congenital anomalies of the kidney and urinary tract, 5 % were post-transplant patients, and only 4 % had chronic glomerulonephritis. The median age was 10.6 years, median height was 133.4 cm, and median weight was 29.2 kg. The median values of serum cysC, average inulin GFR, and maximum inulin GFR were 1.29 mg/dL, 66.3 mL/min/1.73 m^2, and 71.0 mL/min/1.73 m^2, respectively. As it was suspected that urine collection became insufficient in children, we decided to use maximum inulin GFR in the present study.

Correlation of the values obtained from the standardized methods and the standardized values using the correction factor of serum cysC

Figure 2 shows scatter plots of the values obtained from the standardized methods versus the standardized values using the correction factor of serum cysC in the specimen of 86 cases whose frozen serum could be used. The standardized values using the correction factor (y) are shown as the values obtained from the standardized methods (x) as follows—$y = 1.02x - 0.01$, with a correlation coefficient of 0.99, showing a good degree of concordance.

Correlation of 1/serum cysC and maximum inulin GFR

Figure 3 shows scatter plots of maximum inulin GFR versus 1/serum cysC ratio in pediatric CKD patients, including infants and adolescents, which resulted in the equation:

$$\text{maximum inulin GFR} = 104.1 \times 1/\text{serum cysC (mg/L)} - 7.80$$

with a correlation coefficient of 0.869 ($P < 0.01$). The 95% confidence intervals for the slope and intercept were (94.0, 114.3) and (−16.5, 0.9), respectively.

Application of serum cysC-based eGFR formulas for Japanese adults to our materials

Figure 4 shows scatter plots of maximum inulin GFR versus the values obtained with the adult formulas reported by Horio et al. [13] in pediatric CKD patients, including infants and adolescents, which resulted in the equation:

$$\text{maximum inulin GFR} = 1.081 \times \text{cysC-based eGFR values with the adult formula} + 0.398$$

with a correlation coefficient of 0.770 and root mean square error (RMSE) of 17.5. We can say with 95 % confidence that the slope and the intercept lie between 0.979 and 1.182, and between −7.241 and 8.037, respectively. We also calculated a regression line with zero intercept. The slope was 1.086 (95 % confidence interval 1.049 to 1.123), and significantly different from 1.0. The eGFR and measured GFR were 70.1 ± 27.6 and 76.2 ± 34.0, respectively, indicating that eGFR values obtained with the adult formula significantly underestimated GFR by approximately 8 % in children with CKD.

Performance of our new eGFR formula in three age groups, and by gender

Table 2 shows the performance of our new eGFR formula in three age groups, <6 years, 6–11 years, and 12–18 years, and by gender. Bias is the absolute value of measured GFR by the inulin clearance method minus eGFR and is reported as mean ± standard deviation, P_{30} refers to percentage of GFR estimates that are within 30 % of measured GFR, with 95 % confidence intervals given in parentheses, and the RMSE is calculated to show differences between our new eGFR and actual measured GFR values. Figure 5 shows the RMSE among measured maximum inulin GFR and eGFR obtained using our new formula in CKD patients aged <6 years, 6–11 years, and 12–18 years, showing males by rhombus and females by square. RMSE was slightly higher in children aged 12–18 years than in those aged <6 or 6–11 years.

Discussion

GFR reflects kidney function and is measured by assessment of renal clearance. Although inulin clearance is the gold standard for evaluation of kidney function, it cannot be measured easily. Therefore, other methods have been used to assess kidney function, including measurements of cysC concentration. Factors such as renal transplantation, glucocorticoid use, and malignancy, may affect serum

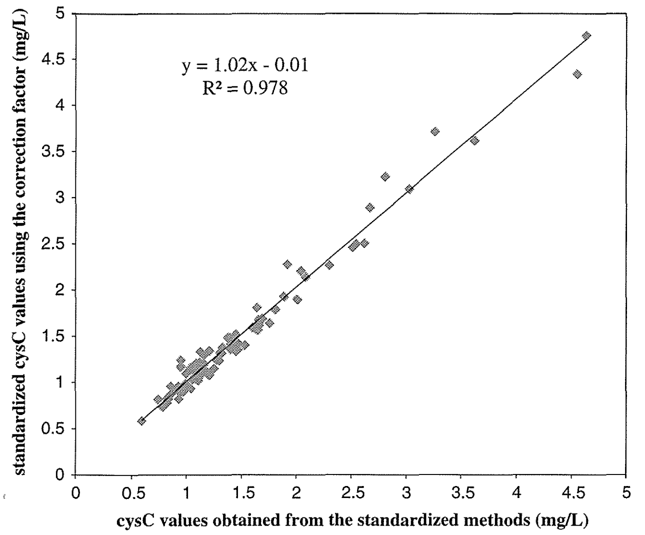

Fig. 2 Correlation of the values obtained from the standardized methods and the standardized values using the correction factor of serum cysC. Standardized values using the correction factor (y) are shown as the values obtained from the standardized methods (x) as follows—$y = 1.02x - 0.01$, with a correlation coefficient of 0.99, showing a good degree of concordance

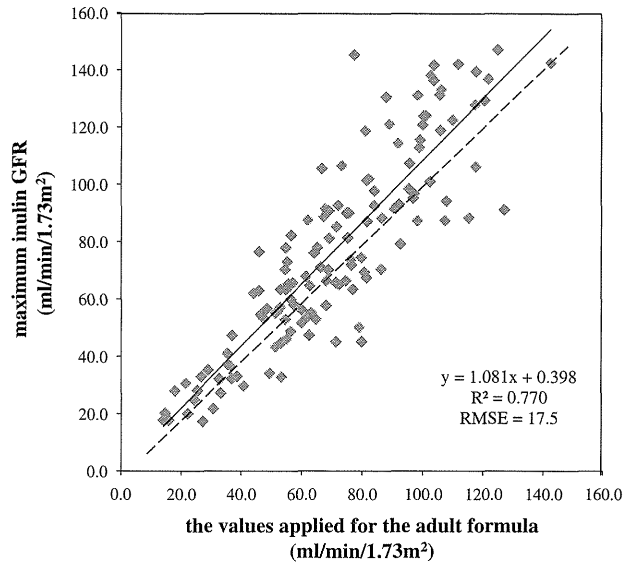

Fig. 4 Analysis of the cysC-based eGFR values obtained with the adult formula and maximum inulin GFR in pediatric CKD patients, including infants and adolescents. *Dashed lines* show the fit of the data. The regression equation was $y = 1.081x + 0.398$. The eGFR values obtained with Horio's adult formula in children with CKD were slightly different from the inulin GFR values

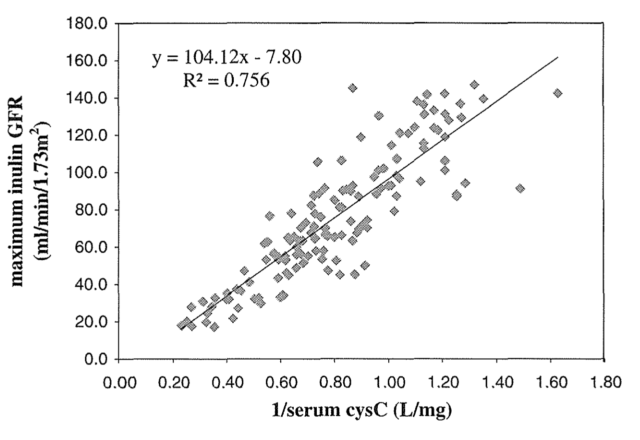

Fig. 3 Analysis of 1/serum cysC and maximum inulin GFR in pediatric CKD patients, including infants and adolescents. The regression equation was $y = 104.12x - 7.80$. A significant positive correlation was observed in 135 children and adolescents with CKD, with a correlation coefficient of 0.869

cysC concentration independent of GFR [14–18] Nevertheless, cysC concentration is regarded as more accurate than the measurement of serum Cr for determining kidney function, because serum Cr level shows a significant positive correlation with body length in children [19, 20], and because low serum Cr concentrations have been reported in selected populations of children with low muscle mass. In contrast, cysC concentration was found not to vary with age, height, or gender [21–23]. Moreover, cysC-based equations may more precisely estimate GFR than Cr-based equations in pediatric patients, [14, 24–26] although these equations may be cumbersome to use in clinical practice because of their complicated formulas and/ or the need for logarithmic transformation of variables. However, these formulas are not designed for the Japanese population, and because of ethnic differences in renal function it is necessary to establish a specialized cysC-based eGFR equation for use in Japanese children.

We reported previously that the new Schwartz 'bedside' Cr-based formula cannot be used to estimate GFR in Japanese children [27], and we developed simple and complicated eGFR equations for use in Japanese children aged 2–11 years [3] and 2–18 years [4]. However, these equations must be adjusted to parameters of body length, and have the limitation complication of muscle mass. Conversely, serum cysC concentrations do not require adjustments for body length, are not complicated by muscle mass, and estimate GFR as a single-sample measurement. In addition, the serum Cr-based formulas cannot be used in children <2 years because GFR varies to some extent among children, increasing from approximately 30−100 % of the level in adults during the first 2 years after birth. However, the serum cysC-based formula can be used, thus making serum cysC measurement a more attractive marker for GFR for use in clinical practice.

We reported reference serum cysC values in Japanese children obtained by four different assays [28]. The serum cysC was measured using 4 different assays in 1,133 Japanese children aged 1 month to 16 years without kidney disease. The serum concentrations of cysC in children were

Table 2 Performance of the GFR-estimating equation in all 135 subjects

Age	All ($n = 135$)	Aged <6 years ($n = 21$)	12 years > aged ≥ 6 years ($n = 59$)	Aged ≥ 12 years ($n = 55$)
Bias (mL/min/1.73 m^2)	12.6 ± 11.1	11.7 ± 8.3	10.7 ± 9.5	15.0 ± 13.1
P_{30} (%)	84 (76–90)	81 (58–95)	90 (79–96)	78 (65–88)
Root mean square error (mL/min/1.73 m^2)	16.9	13.3	13.7	19.7
Gender		All ($n = 135$)	Male ($n = 88$)	Female ($n = 47$)
Bias (mL/min/1.73 m^2)		12.6 ± 11.1	12.6 ± 11.1	12.5 ± 11.2
P_{30} (%)		84 (76–90)	90 (81–95)	72 (57–84)
Root mean square error (mL/min/1.73 m^2)		16.9	16.5	15.9

Bias is the absolute value of mGFR minus eGFR and is reported as mean ± standard deviation; P_{30} refers to percentage of GFR estimates that are within 30% of mGFR, with 95% confidence intervals given in parentheses

eGFR estimated glomerular filtration rate, *mGFR* glomerular filtration rate measured by inulin clearance method

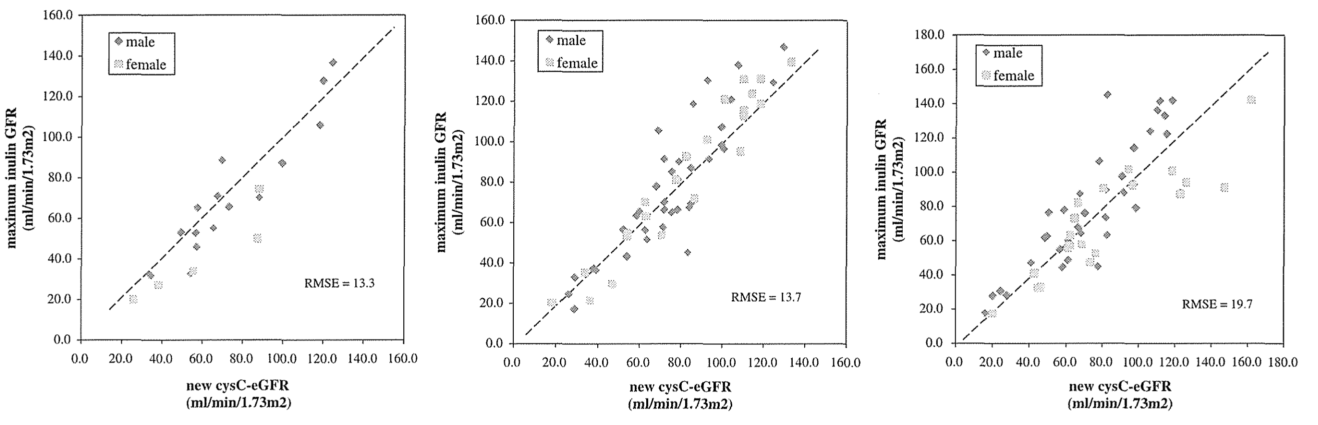

Fig. 5 Analysis of the new cysC-based eGFR and maximum inulin GFR in pediatric CKD patients. *Left* in CKD patients aged <6 years. *Center* in CKD patients aged 6–11 years. *Right* in CKD patients aged ≥12 years. *Dashed lines* show the fit of the data. RMSE was slightly higher in children aged 12–18 years than <6 or 6–11 years

constant after the first postnatal 18 months with a slight decrease in the pubertal period. Standardization of serum cysC measurements was required among children and adults for it to be used as a reliable biomarker. In 2011, the standardized method of cysC measurement traceable to ERM-DA471/IFCC became available. In the present study, serum cysC values were measured by the colloidal gold immunoassay, one of the assays in which standardization was achieved before 2011, and calibrated to the standardized value similar to the method of Horio et al. [13].

Furthermore, we reported that serum cysC concentrations lead to underestimation of renal dysfunction compared with serum Cr in pediatric patients with CKD when we supposed a simple reciprocal relationship between cysC and GFR, and the existence of non-renal clearance of cysC may explain the result [29]. This result may be explained by the rate of non-renal clearance of cysC, which is approximately 20 mL/min/1.73 m^2 in humans [30]. Therefore, the cysC-based eGFR should be the form suggested by Bökenkamp et al. [14], taking non-renal clearance of cysC into account. From the same viewpoint, Cin and cysC measurements in pediatric CKD patients were used to derive the formula for estimation of GFR from cysC concentrations by linear regression analysis:

$$\text{eGFR}\left(\text{mL/min/1.73 m}^2\right) = 104.1/\text{serum cysC (mg/L)} - 7.80.$$

We showed the values of bias, accuracy (P_{30}) and RMSE of our new formula by age group and gender, and believe that we can use the new cysC-based formula in Japanese pediatric CKD patients of all ages. We also validated the cysC-based eGFR formula for Japanese adults [13]. eGFR values obtained with the adult formula significantly underestimated GFR by approximately 8 % in children with CKD. Therefore, suggest that it is better to evaluate the renal functions of pediatric CKD patients using our new formula than the adult expression.

Our equations derived from serum cysC in Japanese children and adolescents, including infants, will be useful for estimating their renal function. Limitations of our study include the small number of subjects, especially <2 years and females, and no other data set to validate the equations. Therefore, further studies are required to validate our equations using different data sets.

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Conflict of interest The authors declare there are no conflicts of interest.

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ORIGINAL ARTICLE

Creatinine-based equations to estimate glomerular filtration rate in Japanese children aged between 2 and 11 years old with chronic kidney disease

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Abstract
Background Renal inulin clearance is the gold standard for glomerular filtration rate (GFR), but is compromised by problems of collecting urine samples in children, especially those <6 years of age or with a bladder dysfunction. Therefore, we should utilize the serum creatinine (Cr)-based estimated GFR (eGFR), measuring serum Cr by enzymatic method. The updated Schwartz formulae were reported by enzymatic Cr instead of by the Jaffe method in American children aged 1–16 years old. We believe it would be better to determine serum Cr-based eGFR by the enzymatic method in Japanese children for evaluation of renal function.
Methods Serum Cr-based eGFR was determined by measuring inulin clearance and serum Cr level in 76 pediatric chronic kidney disease (CKD) patients (49 males and 27 females) aged 2–11 years with no underlying disease that would affect renal function.
Results We showed the inulin clearance by expression of the body length/serum Cr ratio in pediatric CKD patients, which resulted in the equation: inulin GFR $= 0.342 \times$body length (cm)/serum Cr (mg/dL) $\pm$ 2.75. Additionally, we suggest the following serum Cr-based eGFR formula passing through the origin: eGFR $(\mathrm{mL/min/1.73\,m^2})$ $= 0.35 \times$ body length (cm)/serum Cr (mg/dL), because it is simple and easy to remember, thus making it clinically useful.
Conclusion The new eGFR formula derived from body length and serum Cr level is applicable for clinical screening of renal function in Asian as well as Japanese children aged between 2 and 11 years old.

Keywords Estimate glomerular filtration rate · Japanese children · Creatinine-based equation · Chronic kidney disease

Introduction

Serum creatinine (Cr) levels are generally proportional to muscle mass and inversely proportional to renal function. Therefore, they are lower in infancy, and increase gradually with growth. Schwartz et al. [1] expressed the relationships between body length, glomerular filtration rate (GFR), and serum Cr level as estimated GFR (eGFR: mL/min/1.73 m^2) $= k \times$ body length (cm)/serum Cr value (mg/dL). The coefficient k is 0.33 in preterm infants <1 year old, 0.45 in full-term infants <1 year old, 0.55 in children 2–12 years old, and 0.55 and 0.70 in females and males >12 years old, respectively [1–4].

This formula is clinically useful as it allows estimation of GFR from the patient's body length and serum Cr. This equation utilizes the Jaffe method to measure Cr. However, enzymatic methods have recently been used to measure Cr, making the above formula no longer applicable. In 2009, the updated Schwartz formulas were reported as—eGFR (mL/min/1.73 m^2) $= 0.413 \times$ body length (cm)/serum Cr value (mg/dL), and eGFR (mL/min/1.73 m^2) $= 39.1 \times$ [body length (m)/serum Cr (mg/dL)]$^{0.516} \times$ [1.8/cystatin C (mg/L)]$^{0.294} \times$ [30/BUN (mg/dL)]$^{0.169} \times$ [1.099]$^{\mathrm{male}} \times$ [body

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length (m)]/1.4]$^{0.188}$ by enzymatic Cr determination in children 1–16 years old [5].

We doubt whether the new Schwartz equations can be used to estimate GFR in Japanese children with chronic kidney disease (CKD), because there are differences in renal function and muscle mass between Japanese and American individuals. In addition, it is inconclusive whether one common 'bedside' equation can be used in children between 1 and 16 years of age, including the period of adolescence. Therefore, we attempted to derive formulas to estimate GFR by enzymatic Cr determination in Japanese children with CKD. It is clinically important for general pediatricians as well as pediatric nephrologists to measure the eGFR of pediatric CKD patients, as it allows them to evaluate their renal function and provide optimal medical care.

We have determined reference serum Cr levels by an enzymatic method related to age, gender, and body length, and linear and polynomial equations showing the relationship between body length and serum Cr level for screening of renal function in Japanese children [6, 7]. The present study was performed to derive a serum Cr-based eGFR equation in Japanese children aged between 2 and 11 years, with serum Cr levels inversely proportional to renal function.

Table 1 Baseline characteristics of 174 children

Characteristics	*N*
Total	174
Age (years)	
<6	33
≥ 6 and <12	67
≥ 12	74
Gender	
Male	113
Female	61
Renal abnormality	
Congenital anomalies of the kidney and urinary tract	69
Reflux nephropathy	19
Idiopathic nephrotic syndrome	16
Neurogenic bladder	10
Renal transplant	9
Chronic glomerulonephritis	8
Polycystic kidney disease	6
Nephronophthisis	6
Alport syndrome	4
Miscellaneous	27

Materials and methods

Study population

A total of 174 children (113 males and 61 females) between the ages of 1 month and 18 years presenting at the facilities of the members for the Committee of Measures for Pediatric CKD between 2008 and 2011 with CKD were included in this study (Table 1). The study was approved by the local ethics boards of each institution, and written informed consent was obtained from the parents of each subject.

GFR and serum Cr measurements

Data regarding serum Cr values, renal inulin clearance (Cin), and body length measured at the same time were reviewed.

The GFR was measured with inulin [8, 9]. Cin was measured from samples taken twice over a 2–h period under fasting and hydrated conditions by the continuous infusion method (Fig. 1). The children were fasted overnight and were allowed only water after waking up in the morning. First, they received an intravenous Ringer's solution load of 20 mL/kg body weight for 30 min to obtain good diuresis, followed by a load of 5 mL/kg/h until testing was completed. From 30 min after water loading, inulin was given intravenously in a priming dose of 40 mg/kg body weight for 30 min calculated to achieve an extracellular fluid (ECF) level of 20 mg/dL. After the priming dose, inulin was administered at a rate calculated to maintain a constant level in the blood [9]. For this purpose, the rate of inulin infusion must equal that of loss in the urine. To calculate inulin loss, GFR was estimated from serum creatinine by the Schwartz formula [1–4]. Therefore, the patients received an inulin load of $0.7 \times$ eGFR mL/m^2/h with calculation of the body surface area by the Haycock method [10]. Urine samples were collected in two periods of 1 h each, and blood samples were obtained twice from an indwelling cannula in the middle of urine collection. We collected urine samples of children <6 years old or with bladder dysfunction by indwelling catheters.

Serum samples were stored at −70 °C until serum Cr was measured by SRL Inc. (Tokyo, Japan). The serum Cr level was determined by an enzymatic method using a Bio Majesty automated analyzer (JCA-BM8060; JEOL Inc., Tokyo, Japan) with Pure Auto S CRE-L (Sekisui Medical Co., Ltd., Tokyo, Japan). The coefficient of variation was satisfactory (2.08 %). Urine and serum samples were stored at 4 °C until urine and serum inulin were measured by SRL Inc. The urine and serum levels of inulin were determined by an enzymatic method using an automated analyzer (Hitachi 7170; Hitachi Ltd., Tokyo, Japan) with Dia-color-inulin (Toyobo Co., Ltd.,

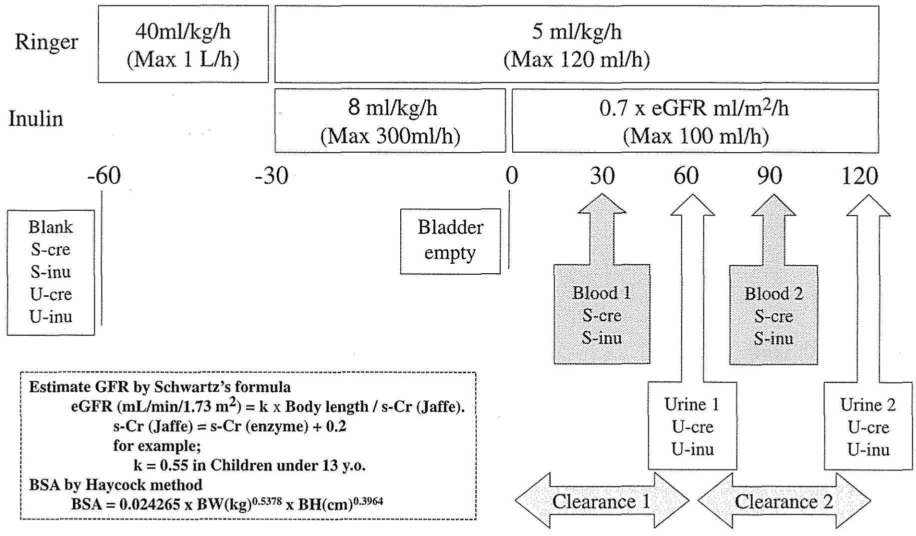

Fig. 1 Inulin clearance method standardized according to the Committee of Measures for Pediatric CKD. Inulin was given intravenously to achieve extracellular fluid levels of 20 mg/dL in testing. For this purpose, the rates of inulin infusion must equal the rates of loss in the urine, which were calculated using the Schwartz formulas based on serum Cr level

Tokyo, Japan). The coefficient of variation was satisfactory (<15 %).

Estimated GFR based on serum Cr

Reference serum Cr level (y) was expressed as a linear equation of body length (x), and the regression equation was $y = 0.30x$ [6, 7] in Japanese children between 2 and 11 years old. As the reciprocal of serum Cr is generally correlated with GFR [1–5, 11], we could utilize the equation for eGFR derived from serum Cr, eGFR (%) = (reference serum Cr/patient's serum Cr) × 100. Therefore, we derived the GFR estimation expression for Japanese children from serum Cr—eGFR (mL/min/1.73 m^2) = k × body length/serum Cr.

Exclusion criteria and cases that were excluded

In this study, the exclusion criteria were (a) severe obstructive uropathy; (b) infection during treatment; (c) inflammatory disease; (d) dehydration; (e) myopathy; (f) severe cardiac, hepatic, or pancreatic disease; (g) pregnancy or the possibility of pregnancy; (h) nursing; and (i) refusal or inability to give informed consent. Infants <2 years old and children >11 years old were excluded because of low GFR compared with adults [12] and the sharp increase in muscle mass in puberty [4, 7, 13], respectively. One case with myopathy was excluded because of violation of the protocol. In this study, doses of intravenous inulin administration were decided as blood concentrations were constant during testing by calculating the eGFR by the Schwartz formula. Therefore, cases in which the ratios of urine inulin excretion and intravenous inulin administration were <0.5 or >1.5 were excluded from this study, because there may have been failure to collect all urine. As we were interested in determining eGFR of cases with GFR <120 mL/min/1.73 m^2, we excluded cases with GFR >150 mL/min/1.73 m^2 to increase reliability.

Statistical analyses

All analyses were conducted using Microsoft Excel 2010 and the JMP 8 statistical software package (SAS Institute Inc, Cary, NC, USA). Linear regression analyses were performed to evaluate relations between the ratios of body length/serum Cr and Cin. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Results

Characteristics of the study population

Of the 174 children included in the study, 65 % were male, 40 % had congenital anomalies of the kidney and urinary tract, 5 % were post-transplant patients, and only 5 % had chronic glomerulonephritis (Table 1). The median age was 11.0 years.

Infants <2 years old and children >11 years old were excluded, and 91 CKD patients aged between 2 and 11 years were initially included in the study population. One case with myopathy was excluded because of protocol violation. Thirteen cases with ratios of urine inulin excretion and intravenous inulin administration <0.5 or >1.5, and one case with GFR >150 mL/min/1.73 m^2 were also excluded.

Therefore, a total of 76 cases (49 males) were included in this study (Table 2). The median age was 8.0 years, median height was 115.8 cm, and median weight was

Table 2 Characteristics of 76 children included in this study

Characteristics	Median (IQR)	*n*
Total		76
Age (years)	8.0 (6.1–9.8)	
<6		17
≥6 and <12		59
Gender		
Male		49
Female		27
Body length (cm)	115.8 (108.7–128.2)	
Body weight (kg)	21.3 (17.1–27.0)	
BSA (m^2)	0.83 (0.72–0.97)	
Serum creatinine (mg/dL)	0.57 (0.42–0.73)	
Average inulin GFR (mL/min/1.73m^2)	65.4 (45.9–94.2)	
Maximum inulin GFR (mL/min/1.73m^2)	70.2 (53.1–99.2)	

IQR interquartile range, *BSA* body surface area

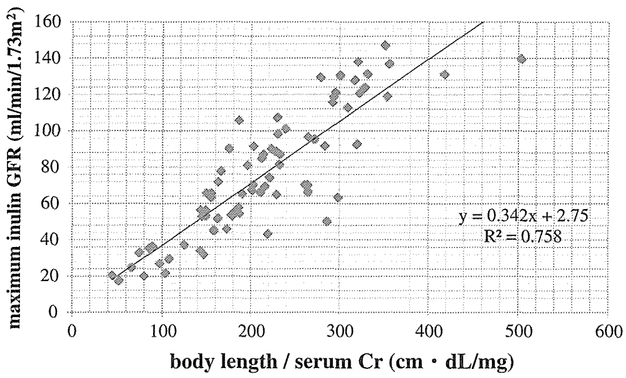

Fig. 2 Analysis of body length/serum Cr and maximum inulin GFR in pediatric CKD patients aged between 2 and 11 years. The regression equation was $y = 0.342x + 2.75$. A significant positive correlation was observed in 76 children with CKD aged 2–11 years old, with a correlation coefficient of 0.871

21.3 kg. The median values of serum Cr, average inulin GFR, and maximum inulin GFR were 0.57 mg/dL, 65.4 mL/min/1.73 m^2, and 70.2 mL/min/1.73 m^2, respectively. As it was suspected that urine collection became insufficient in children, we decided to use maximum inulin GFR in the present study.

Correlation of body length/serum Cr and maximum inulin GFR

Figure 2 shows scatter plots of maximum inulin GFR versus body length/serum Cr ratio in pediatric CKD patients aged between 2 and 11 years, which resulted in the equation:

$$\text{Maximum inulin GFR} = 0.342 \times \text{body length (cm)}/\text{serum Cr (mg/dL)} + 2.75$$

with a correlation coefficient of 0.871 ($P < 0.01$).

Serum Cr-based eGFR formula in pediatric CKD patients aged between 2 and 11 years

We would like to suggest use of the formula passing through the origin for children aged 2–11 years old, because it is simple and easy to remember for use at the bedside. We developed an eGFR equation for Japanese children aged between 2 and 11 years as follows:

$$\text{eGFR (mL/min/1.73 m}^2) = 0.35 \times \text{body length (cm)}/\text{serum Cr (mg/dL)}.$$

We compared our new formula with the correlation equation (maximum inulin GFR = 0.342 × body length/serum Cr + 2.75) in our CKD patients. Maximum and minimum differences between eGFR values calculated by these two equations in all 76 cases were 1.28 and −2.39 mL/min/1.73 m^2, respectively. Thus, the eGFR values derived from the two equations showed good accordance.

Discussion

Glomerular filtration rate is used to assess kidney function and is measured by monitoring renal clearance. Inulin clearance is the gold standard for evaluation of kidney function but cannot be measured easily. Therefore, various methods have been used to determine GFR. The eGFR [eGFR (mL/min/1.73 m^2) = k × body length (cm)/serum Cr (mg/dL)] determined by the Jaffe method devised by Schwartz has been used clinically [1–4]. Recently, enzymatic methods have been used to measure Cr rather than the Jaffe method; however, it is not possible the use the formula in this form and it was necessary to reevaluate the value of the coefficient k in the formula. Recently, Zappitelli et al. [14] revised the Schwartz formula relating eGFR to serum creatinine level determined enzymatically, and reported that the k value in the Schwartz equation decreased from 0.55 to 0.47 for children and adolescent girls. Schwartz et al. [5] reported the updated formula, the so-called 'bedside' version, as eGFR = 0.413 × body length (cm)/serum Cr value (mg/dL) by the enzymatic method showing a 25 % reduction in k value from the previous value of 0.55 generated from Jaffe-based serum Cr measurements, and eGFR(mL/min/1.73 m^2) = 39.1 × $[\text{body length (m)}/\text{serum Cr (mg/dL)}]^{0.516} \times [1.8/\text{cystatin C (mg/L)}]^{0.294} \times [30/\text{BUN (mg/dL)}]^{0.169} \times [1.099]^{\text{male}} \times [\text{body length (m)}/1.4]^{0.188}$ by enzymatic Cr determination in children 1–16 years old. The work was performed in a population of American children with CKD, enriched with obstructive uropathy. They concluded that the formula can be used in children 1–16 years old.

However, we reported previously that the new Schwartz 'bedside' formula cannot be used for estimating GFR in Japanese children, especially those between 1 and 16 years old including the adolescent period, as reference serum Cr values of our 1,074 subjects [7] showed a gradual significant decrease of eGFR with age [13]. There seems to be a considerable problem in that the ranges of the reference values for boys >12 years and girls >14 years overlap with the range for CKD stage 2. Our results indicating that eGFR value derived by the new 'bedside' Schwartz formula decreased gradually with age suggest that this formula should not be used for estimating GFR in Japanese children, at least in those with normal renal function.

The new 'bedside' Schwartz formula has an inherent problem in that it uses the same coefficient between the ages of 1 and 16 years old. In addition, we assume that renal function and muscle mass show ethnic differences. Therefore, it is necessary to establish a specialized eGFR equation for use in Japanese children.

We examined the correlation of body length/serum Cr and maximum inulin GFR in Japanese children aged between 2 and 11 years old and derived the equation: $\mathrm{eGFR} = 0.342 \times (\text{body length/serum Cr}) + 2.75$. Therefore, we suggest a new formula derived from body length and serum Cr in Japanese children aged between 2 and 11 years old as follows:

$$\mathrm{eGFR}\ (\mathrm{mL/min/1.73\,m^2}) = 0.35 \times \text{body length (cm)} / \text{serum Cr (mg/dL)}.$$

These two equations showed good accordance in our cases, and we adopted the formula passing through the origin because it is simple and easy to remember, thus making it clinically useful. Further studies are required to validate our equations using a different data set. In our next study, we would like to present complex eGFR equations using polynomial formulae for reference serum Cr levels with body length in Japanese all children and adolescents except infants. We consider that the formula will be applicable for screening of renal function in Asian as well as Japanese children between the ages of 2 and 11 years old.

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はじめよう、検査説明

〔一般検査 12〕

小児の腎機能は大人とどう違うのですか？
また，検査評価法を教えてください

上村　　治

臨　床　検　査
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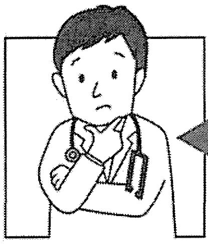
2013 年 10 月 30 日　発行

医学書院

臨床医からの質問



小児の腎機能は大人とどう違うのですか？ また，検査評価法を教えてください

1．腎機能の成熟

新生児期の GFR は成人の 1/5 程度ではじまり，2 歳前に成人とほぼ同等となる．そのため例えば血清クレアチニン基準値は生後数カ月まで減少するが，その後は筋肉量の成長とともに増加する．

2．小児の血清クレアチニン基準値（表 1，2，図 1）

血清クレアチニン値（SCr）は，腎機能に反比例し，筋肉量に比例する．小児の SCr 基準値の生理的な推移は，出生直後は母親と同値であるが数日後には本人の値である 0.4 mg/dL 程度，腎機能の発達とともに 1 歳台 0.2 mg/dL 強，身長の伸びに合わせて 4 歳 0.3 mg/dL，10 歳 0.4 mg/dL となり，その後思春期の急激な筋肉量の増加に合わせて急上昇し，成人するころには男性 0.8 mg/dL，女性 0.6 mg/dL 程度になる．

3．小児の血清シスタチン C 基準値と β_2 ミクログロブリン基準値

血清シスタチン C（cysC）測定は標準化された．小児の cysC 基準値（表 3，4）の生理的な推移は腎機能の発達とともに変化し，新生児期や乳児期早期は 1.5 mg/L 程度から始まり，腎機能の発達とともに生後 3 カ月 1.1 mg/L 程度，1 歳で 0.9 mg/L 程度，2 歳ではほぼ成人同様の 0.8 mg/L 程度となり，その後思春期後半に 0.7 mg/L 程度に下がる．cysC 値は腎機能が悪化すると上昇スピードが鈍くなり，SCr と異なり腎機能と反比例しない[1)]．

小児の血清 β_2 ミクログロブリン（β_2MG）基準値の生理的な推移は，cysC 同様腎機能の発達とともに変化する．しかし，2 歳以降も徐々に低下する傾向がある．日本人小児の各年齢の β_2MG 基準値[2)]を検討したところ，生後 3 カ月 1.8 mg/L 程度，1 歳で 1.7 mg/L 程度，2 歳で 1.5 mg/L 程度，10 歳で 1.3 mg/L 程度，思春期後半に 1.2 mg/L 程度に下がる．

4．小児の eGFR（推算 GFR）

これまでに小児の GFR を推算するためのいくつかの式が作られたが，酵素法による日本人小児のものはなかった．eGFR を％表示で表すと，

eGFR（%）＝（SCr 基準値/患者の SCr 値）×100

となる．上記の年齢当たりまたは身長当たりの基準値を使えば eGFR（%）は推算できる．

2 歳以上 11 歳以下の小児の eGFR（mL/min/1.73 m^2）は，下記のとおり表される[3)]．

eGFR（mL/min/1.73 m^2）

＝0.35×身長（cm）/患者の SCr 値

乳幼児を除く 2 歳から 18 歳の全年齢について男女別の SCr を使用したものや，全年齢小児の cysC を使用したものは近い将来使用可能となる．

SCr を使用した eGFR は，筋肉量の少ない状態（寝たきりや低栄養など）や筋肉量の多い状態（スポーツ強化選手など）で評価を誤る．その場合，cysC 値や，クレアチニンクリアランス，イヌリンクリアランスで評価する．小児には成人の推算式は適用できない．

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上村　治
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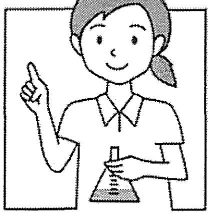


小児の腎機能

小児血清クレアチニン基準値

▼表1　3カ月以上12歳未満(男女合わせて)　(mg/dL)

年月齢	n	2.5%	中央値(50.0%)	97.5%
3～5カ月	18	0.14	0.20	0.26
6～8カ月	19	0.14	0.22	0.31
9～11カ月	31	0.14	0.22	0.34
1歳	70	0.16	0.23	0.32
2歳	73	0.17	0.24	0.37
3歳	88	0.21	0.27	0.37
4歳	81	0.20	0.30	0.40
5歳	96	0.25	0.34	0.45
6歳	102	0.25	0.34	0.48
7歳	85	0.28	0.37	0.49
8歳	56	0.29	0.40	0.53
9歳	36	0.34	0.41	0.51
10歳	44	0.30	0.41	0.57
11歳	58	0.35	0.45	0.58

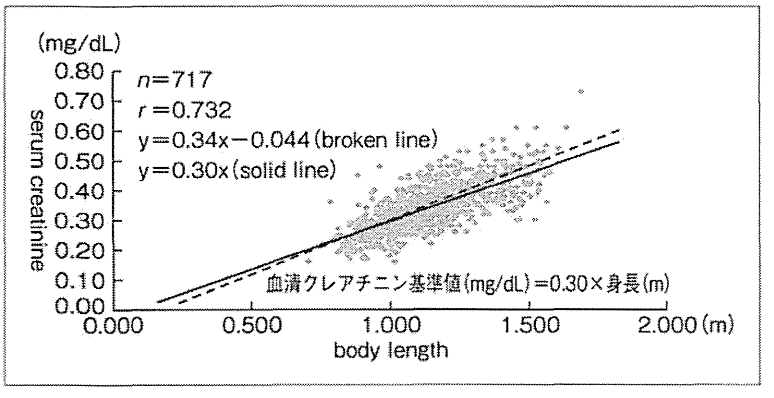
▼表2　12歳以上17歳未満(男女別)　(mg/dL)

性別	男性				女性			
年齢	n	2.5%	中央値(50.0%)	97.5%	n	2.5%	中央値(50.0%)	97.5%
12歳	15	0.40	0.53	0.61	54	0.40	0.52	0.66
13歳	30	0.42	0.59	0.80	38	0.41	0.53	0.69
14歳	17	0.54	0.65	0.96	40	0.46	0.58	0.71
15歳	15	0.48	0.68	0.93	22	0.47	0.56	0.72
16歳	30	0.62	0.73	0.96	27	0.51	0.59	0.74

〔Uemura O, Honda M, Matsuyama T, et al : Age, gender, and body length effects on reference serum creatinine levels determined by an enzymatic method in Japanese children: a multicenter study. Clin Exp Nephrol　15 : 694-699, 2011 より転載〕

2歳以上11歳以下の血清クレアチニン

▼図1



- 2歳以上11歳以下の血清クレアチニン基準値：SCr基準値(mg/dL)=0.30×身長(m).
- 図では示していないが，全年齢を男女に分けて身長の5次式でSCr基準値を推算する式を作成した．男性で $y=-1.259x^5+7.815x^4-18.57x^3+21.39x^2-11.71x+2.628$，女性で $y=-4.536x^5+27.16x^4-63.47x^3+72.43x^2-40.06x+8.778$ であった〔y：推算基準SCr値，x：身長(m)〕.

小児血清シスタチンC基準値(標準化後)

▼表3　3カ月以上12歳未満(男女合わせて)

年月齢	n	2.5%	中央値(50.0%)	97.5%
3～5カ月	18	0.88	1.06	1.26
6～11カ月	47	0.72	0.98	1.25
12～17カ月	31	0.72	0.91	1.14
18～23カ月	38	0.71	0.85	1.04
2～11歳	704	0.61	0.78	0.95

▼表4　12歳以上17歳未満(男女別)

性別	男性				女性			
年齢	n	2.5%	中央値(50.0%)	97.5%	n	2.5%	中央値(50.0%)	97.5%
12～14歳	61	0.71	0.86	1.04	132	0.61	0.74	0.91
15～16歳	45	0.53	0.75	0.92	49	0.46	0.61	0.85

〔Yata N, Uemura O, Honda M, et al : Reference ranges for serum cystatin C measurements in Japanese children by using 4 automated assays. Clin Exp Nephrol, 2013 Feb 28, *in press* より転載〕

日児腎誌 Vol. 26 No. 2

統計調査委員会報告

2006年～2011年末までの期間中に新規発生した20歳未満の小児末期腎不全患者の実態調査報告

日本小児腎臓病学会統計調査委員会[1]，同小児末期腎不全調査小委員会[2]，調査プロトコール作成委員会[3]，調査統計解析[4]，調査データセンター[5]

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緒　　言

小児末期腎不全(ESKD)患者の実態を大規模な疫学調査により評価することは，小児慢性腎臓病(CKD)対策の点からも必須な事項であり[1)2)]，日本小児腎臓病学会の重要な責務の一つである。

日本小児腎臓病学会による小児ESKD患者の実態調査は1999年に開始され，1998年1月1日～同年12月31日末の期間中に発生した20歳未満の小児ESKD例が調査された[3)]。20歳未満の小児を対象とした調査は2000年にも実施(1999年1月1日～同年12月31日末の期間中に発生した小児ESKD例の調査)された[4)5)]。2001年からは，調査対象を15歳未満の小児に引き下げて各年の新規発生例の把握と1998年以降の新規発生例の2005年12月末までの追跡調査が実施され，このうち2003年末までのまとめが報告されている[6)7)]。

しかし，2006年以降の調査が中断されていたため，2007年6月に日本小児腎臓病学会内に統計調査委員会が新たに設立され，2006年以降の小児ESKD患者実態把握調査をどのようにすればよいかについての検討が始まった[8)]。同時に，1998年～2005年末までの期間に発生した15歳未満のESKD症例の2007年末の状態に関する追跡調査が実施された[9)]。

今回，2006年から2011年末の6年間における20歳未満小児ESKD患者の新規発生数や腎代替療法の選択，生命予後等の実態を把握することを目的として，関連学会の協力のもと日本小児腎臓病学会統計調査委員会が後方視的に全国疫学調査を行ったので，調査結果を報告する。

対象および方法

1. 調査対象施設・診療科

充分な網羅性と実施可能性を勘案し，日本小児腎臓病学会，日本小児腎不全学会，日本小児PD・HD研究会，日本透析医学会，日本臨床腎移植学会のいずれかに登録されている施設・診療科および全国の医学部・医科大学，そして小児病院のうち，小児ESKD患者が診療されている可能性がある施設・診療科を調査対象施設・診療科として設定した。

2. 調査対象症例

調査対象施設・診療科において，2006年から2011年末までの6年間に新規にESKDと診断され，腎代替療法の開始時点で20歳未満の患者を調査対象とした。

ESKD患者は，不可逆的な腎機能障害のため腎代替療法[血液透析(HD)，腹膜透析(PD)，先行的腎移植]を開始した患者，ならびに腎代替療法を選択しなかった患者と定義した。

なお，腎移植後透析(PD，HD)導入例は新規発生例から除外した。