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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

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).

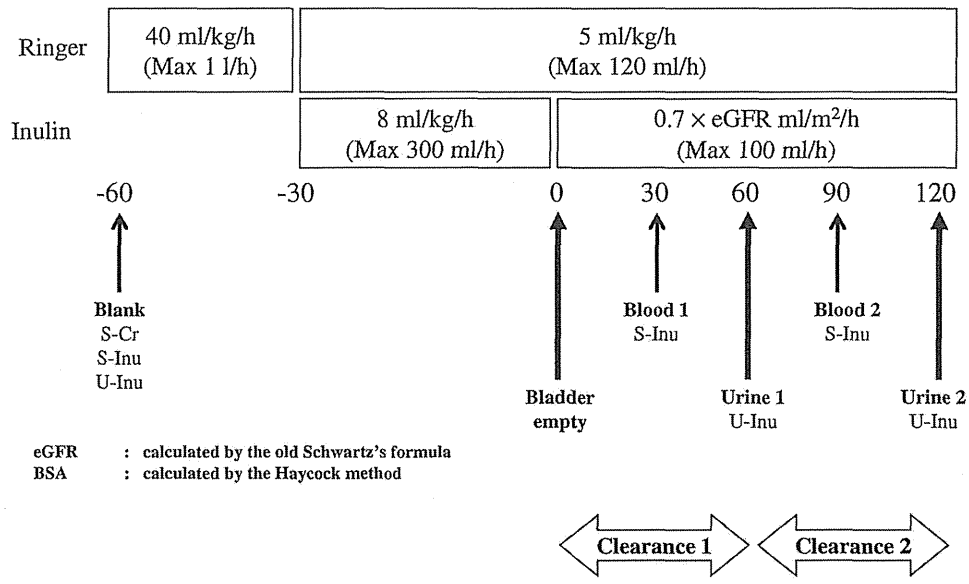

Fig. 1 Inulin clearance method standardized according to the Committee of Measures for Pediatric CKD. Inulin was given intravenously to achieve extracellular fluid levels of 20 mg/dL in testing. For this purpose, the rates of inulin infusion must equal the rates of loss in the urine, which were calculated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

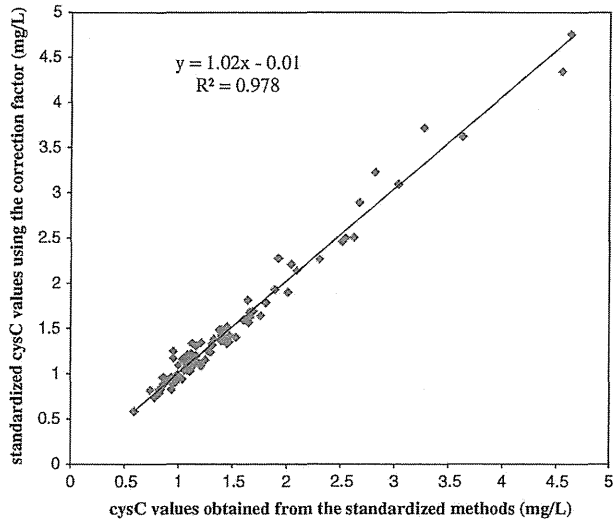

Fig. 2 Correlation of the values obtained from the standardized methods and the standardized values using the correction factor of serum cysC. Standardized values using the correction factor (y) are shown as the values obtained from the standardized methods (x) as follows—$y = 1.02x - 0.01$, with a correlation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

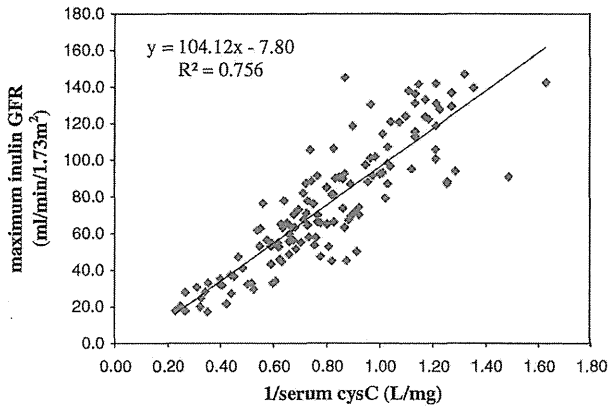

Fig. 3 Analysis of 1/serum cysC and maximum inulin GFR in pediatric CKD patients, including infants and adolescents. The regression equation was $y = 104.12x - 7.80$. A significant positive correlation was observed in 135 children and adolescents with CKD, with a correlation coefficient of 0.869

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]

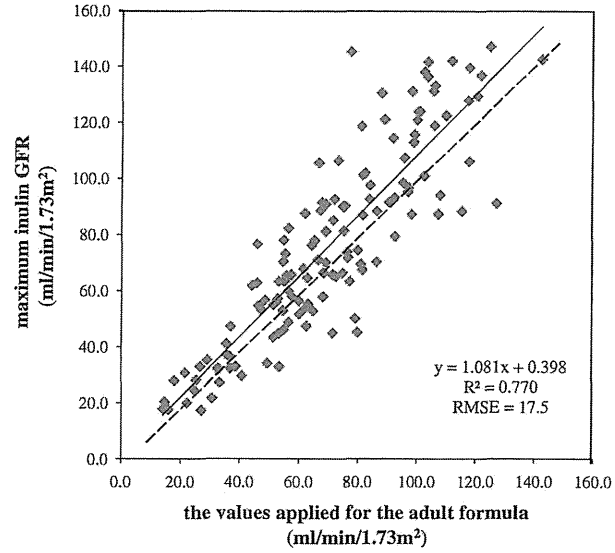

Fig. 4 Analysis of the cysC-based eGFR values obtained with the adult formula and maximum inulin GFR in pediatric CKD patients, including infants and adolescents. *Dashed lines* show the fit of the data. The regression equation was $y = 1.081x + 0.398$. The eGFR values obtained with Horio's adult formula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

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

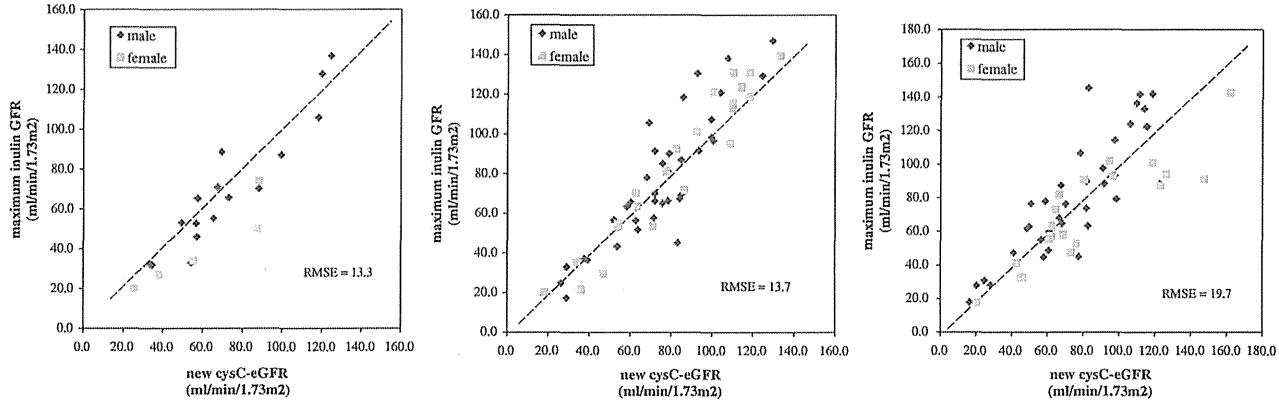

Fig. 5 Analysis of the new cysC-based eGFR and maximum inulin GFR in pediatric CKD patients. *Left* in CKD patients aged <6 years. *Center* in CKD patients aged 6–11 years. *Right* in CKD patients aged ≥12 years. *Dashed lines* show the fit of the data. RMSE was slightly higher in children aged 12–18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

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

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 equation to estimate the glomerular filtration rate in Japanese children and adolescents with chronic kidney disease

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Abstract

Background Renal inulin clearance is the gold standard for evaluation of kidney function, but cannot be measured easily in children. Therefore, we utilize the serum creatinine (Cr)-based estimated GFR (eGFR) measuring serum Cr by the enzymatic method, and we have reported simple serum Cr-based eGFR in Japanese children aged between 2 and 11 years old. Furthermore, we should use serum Cr-based eGFR in Japanese adolescents as well as children with chronic kidney disease for evaluation of renal function.

Methods The inulin clearance and serum Cr level determined by an enzymatic method were measured in 131 pediatric chronic kidney disease (CKD) patients between the ages of 2 and 18 years old with no underlying disease affecting renal function except CKD to determine the serum Cr-based eGFR in Japanese children and adolescents.

Results We offer the complex estimated GFR equation using polynomial formulae for reference serum creatinine levels with body length in Japanese children except infants, resulting in the following equation:

$$\text{eGFR} = 110.2 \times (\text{reference serum Cr}/\text{patient's serum Cr}) + 2.93$$

Reference serum Cr levels (y) are shown by the following two equations of body length (x):

$$\text{Males}: \quad y = -1.259x^5 + 7.815x^4 - 18.57x^3 + 21.39x^2 - 11.71x + 2.628$$

$$\text{Females}: \quad y = -4.536x^5 + 27.16x^4 - 63.47x^3 + 72.43x^2 - 40.06x + 8.778$$

Conclusion The new polynomial eGFR formula showing the relationship with body length and serum Cr level may be applicable for clinical screening of renal function in

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Japanese children and adolescents aged between 2 and 18 years.

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

Introduction

Using renal inulin clearance to measure the glomerular filtration rate (GFR) directly is compromised by problems of collecting urine samples in children, and we should utilize the serum creatinine (Cr)-based estimated GFR (eGFR). Serum 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 relations between body length, GFR, and serum Cr level as estimated GFR (eGFR; ml/min/1.73 m^2) = k × body length (cm)/serum Cr level (mg/dl). The coefficient k is 0.33 in preterm infants under 1 year old, 0.45 in full-term infants under 1 year old, 0.55 in children 2–12 years old, and 0.55 and 0.70 in females and males over 12 years old, respectively [1–4].

This formula is clinically useful as it allows estimation of the normal serum Cr level from the patient's body length. This equation utilizes the Jaffé method to measure Cr. However, enzymatic methods have recently been used to measure Cr, rendering the above formula no longer applicable. In 2009, the updated Schwartz formulae were reported as follows: eGFR (ml/min/1.73 m^2) = 0.413 × body length (cm)/serum Cr level (mg/dl) and eGFR (ml/min/1.73 m^2) = 39.1 × [body length (m)/s-Cr (mg/dl)]$^{0.516}$ × [1.8/cystatin C (mg/l)]$^{0.294}$ × [30/BUN (mg/dl)]$^{0.169}$ × [1.099]^{male} × [body 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 the 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" linear equation can be used in children from 1 to 16 years old, including the period of adolescence. Therefore, we attempted to derive formulae to estimate the glomerular filtration rate by enzymatic Cr determination in Japanese children with CKD.

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 the serum Cr level for screening of renal function in Japanese children [6, 7]. We intended to develop creatinine-based estimated GFR equations using these linear and polynomial equations, with serum creatinine levels being inversely proportional to renal function.

Initially, we developed an estimated GFR equation for 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 × body length (cm)/serum Cr level (mg/dl) [8]. Here, we present a 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.

Materials and methods

Study population

A total of 174 children (113 males and 61 females) between the ages of 1 month and 18 years old presenting at the facilities of the members for the Committee of Measures for Pediatric Chronic Kidney Disease (CKD) between 2008 and 2011 with chronic kidney disease were included. Nevertheless, excluding the cases we describe in detail later, a total of 131 patients (84 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 subject. The ethics committee approval number in Aichi Children's Health and Medical Center is 200810.

GFR and serum Cr measurements

Data regarding serum Cr levels, renal inulin clearance (Cin), and body length measured at the same time were reviewed. The glomerular filtration rate (GFR) was measured with inulin [9, 10]. Cin was measured from samples taken twice over 2 h 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 [10]. 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 old Schwartz

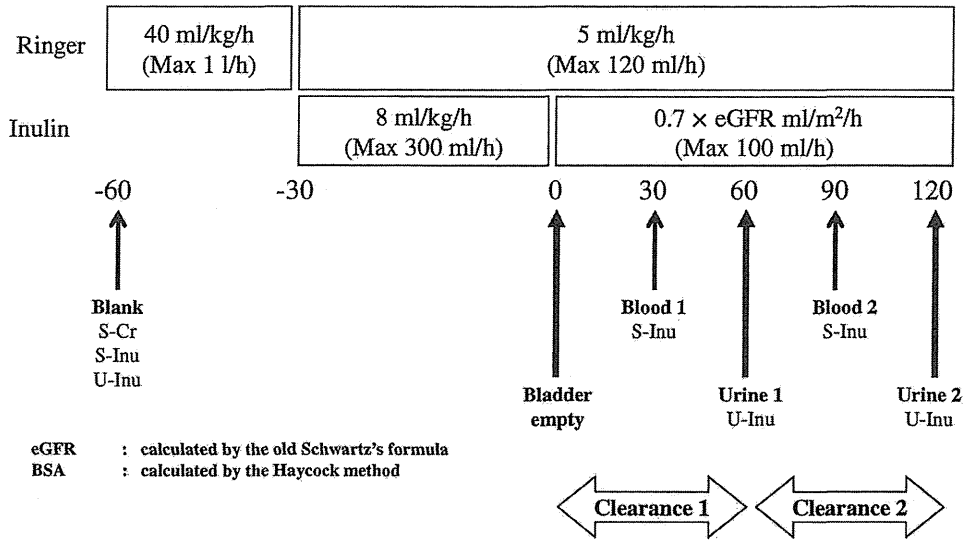

Fig. 1 Inulin clearance method standardized according to the Committee of Measures for Pediatric CKD. Inulin was given intravenously to achieve extracellular fluid levels of 20 mg/dl in testing. For this purpose, the rates of inulin infusion must equal the rates of loss in the urine, which were calculated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

formulae [1–5]. Therefore, the patients received an inulin load of 0.7 × eGFR ml/m^2/h with calculation of body surface area by the Haycock method [11]. 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 under 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 Ltd., Tokyo, Japan) with Pure Auto S CRE-L (Sekisui Medical Co., Ltd., Tokyo, Japan). The coefficient of variation was satisfactory (2.08 %). This method utilizes National Institute of Standards and Technology (NIST) Standard Reference Material 914a as calibration standards similar to isotope dilution mass spectroscopy (IDMS). 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). The coefficient of variation was satisfactory (<15 %).

Estimated GFR based on serum Cr

In Japanese children and adolescents, the reference serum Cr level (y) was expressed as a quintic equation of body length (x), and the regression equations were $y = -1.259x^5 + 7.815x^4 - 18.57x^3 + 21.39x^2 - 11.71x + 2.628$ in males and $y = -4.536x^5 + 27.16x^4 - 63.47x^3 + 72.43x^2 - 40.06x + 8.778$ in females [6]. As the reciprocal of serum Cr is generally correlated with GFR [1–5, 12], we utilized the equation for eGFR derived from serum Cr, eGFR (%) = (reference serum Cr/patient's serum Cr) × 100. Therefore, we derived the following two equations:

$$\text{Males} < 19 \text{ years old: eGFR (\%)} = [(-1.259x^5 + 7.815x^4 - 18.57x^3 + 21.39x^2 - 11.71x + 2.628)/\text{patient's serum Cr}] \times 100$$

$$\text{Females} < 19 \text{ years old: eGFR (\%)} = [(-4.536x^5 + 27.16x^4 - 63.47x^3 + 72.43x^2 - 40.06x + 8.778)/\text{patient's s serum Cr}] \times 100$$

With this report [6], we intend to develop the GFR (ml/min/1.73 m^2) estimation expression for Japanese children by examining relations of GFR (ml/min/1.73 m^2) and reference serum Cr/patient's serum Cr.

Exclusion criteria and cases excluded

In this study, the exclusion criteria were as follows: (1) severe obstructive uropathy; (2) infection during treatment; (3) inflammatory disease; (4) dehydration; (5) myopathy; (6) severe cardiac, hepatic, or pancreatic disease; (7) pregnancy or the possibility of pregnancy; (8) nursing; and (9) refusal or inability to give informed consent. Infants under 2 years old were excluded because of low GFR compared with adults [13]. Three cases (one case with no serum creatinine data and two cases with myopathy) were excluded because of violation of the protocol. In this study, doses of intravenously administered inulin were decided as blood concentrations were constant during testing by calculating the estimated GFR by the old 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 this may have been due to failure to collect all urine. Pediatric patients with chronic kidney disease causing hyperfiltration such as diabetic nephropathy are rare, and we are interested in determining the eGFR of cases with GFR <120 ml/min/1.73 m^2. Therefore, we excluded cases with GFR >150 ml/min/1.73 m^2.

Statistical analyses

All analyses were conducted using Microsoft Excel 2010 and the JMP 10 statistical software package (SAS Institute Inc, Cary, NC, USA). Linear regression analyses were performed to evaluate relations between the ratios of patient's serum Cr/reference serum Cr and Cin in males and females. Differences in the bias (absolute value) of eGFRs were evaluated using paired t tests, and differences in accuracy (i.e., P_{30}) were evaluated using χ^2 tests, similar to the method of Horio et al. [14]. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Results

Characteristics of the study population

Of the 174 children studied, 8 patients under 2 years old, 3 with violation of protocol, 27 whose ratios of urine inulin excretion and intravenous inulin administration were <0.5 or >1.5, and 5 with GFR >150 ml/min/1.73 m^2 were excluded from the study. Therefore, a total of 131 cases (84 males and 47 females) were included in this study (Table 1); 64 % were male, 41 % had congenital anomalies of the kidney and urinary tract (CAKUT), 5 % were posttransplant patients, and only 4 % had chronic glomerulonephritis. The median age was 10.8 years old, median height was 134.5 cm, and median weight was 30.9 kg. The median values of serum Cr, average inulin GFR, and maximum inulin GFR were 0.66 mg/dl, 66.6 ml/min/1.73 m^2, and 71.8 ml/min/1.73 m^2, respectively. As urine collection was suspected to become insufficient in children, we decided to use the maximum inulin GFR in the present study.

Serum Cr-based eGFR formula in pediatric CKD patients aged between 2 and 18 years old

Figure 2 shows scatter plots of maximum inulin GFR versus reference serum Cr/patient's serum Cr ratio in pediatric CKD patients aged between 2 and 18 years old, resulting in the following equation:

Table 1 Characteristics of 131 children included in this study

Characteristics	Median (IQR)	n
Total		131
Age (years)	10.8 (7.5–13.9)	
<6		17
≥6 and <12		59
≥12		55
Gender		
Male		84
Female		47
Renal abnormality		
Congenital anomalies of the kidney and urinary tract		54
Reflux nephropathy		15
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) (years)	134.5 (112.6–152.2)	
<6	98.4 (91.6–110.0)	
≥6 and <12	122.4 (110.6–132.0)	
≥12	154.2 (145.4–162.8)	
Weight (kg) (yeras)	30.9 (19.6–41.9)	
<6	15.4 (12.3–17.7)	
≥6 and <12	24.6 (18.8–28.9)	
≥12	45.3 (37.9–50.7)	
BSA (m^2) (years)	1.04 (0.79–1.32)	
<6	0.65 (0.55–0.74)	
≥6 and <12	0.91 (0.76–1.03)	
≥12	1.38 (1.23–1.51)	
Serum creatinine (mg/dl) (years)	0.66 (0.51–0.90)	
<6	0.56 (0.38–0.66)	
≥6 and <12	0.69 (0.43–0.74)	
≥12	0.97 (0.63–1.05)	
Average inulin GFR (ml/min/1.73 m^2) (years)	66.6 (46.5–93.5)	
<6	58.8 (40.6–73.0)	
≥6 and <12	74.6 (50.0–95.5)	
≥12	71.7 (52.4–91.9)	
Maximum inulin GFR (ml/min/1.73 m^2) (years)	71.8 (53.0–97.4)	
<6	63.9 (46.0–74.4)	
≥6 and <12	80.0 (55.5–106.5)	
≥12	77.0 (53.9–93.6)	

IQR interquartile range

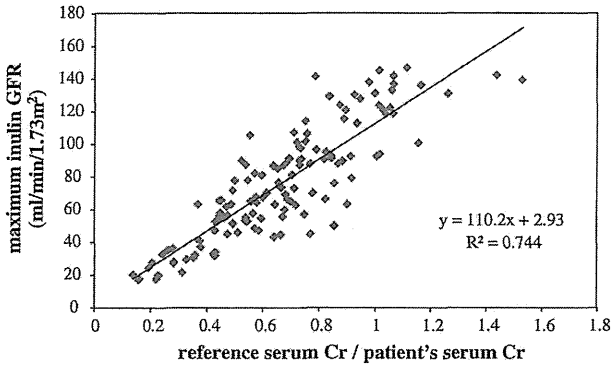

Fig. 2 Analysis of reference serum Cr/patient's serum Cr and maximum inulin GFR in pediatric CKD patients aged between 2 and 18 years old. The regression equation was $y = 110.2x + 2.93$. A significant positive correlation was observed in children with CKD aged between 2 and 18 years old, with a correlation coefficient of 0.863

$$\text{eGFR} = 110.2 \times (\text{reference serum Cr/patient's serum Cr}) + 2.93$$

Reference serum Cr levels (y) are shown by the following two equations of body length (x):

$$\text{Males}: \quad y = -1.259x^5 + 7.815x^4 - 18.57x^3 + 21.9x^2 - 11.71x + 2.628$$

$$\text{Female}: \quad y = -4.536x^5 + 27.16x^4 - 63.47x^3 + 72.43x^2 - 40.06x + 8.778$$

Correlation between two serum Cr-based eGFR formulae in pediatric CKD patients aged between 2 and 11 years old

We developed an estimated GFR equation for use in Japanese CKD patients aged between 2 and 11 years old as follows: eGFR (ml/min/1.73 m^2) = 0.35 × body length (cm)/serum Cr level (mg/dl) [6].

We compared our new formula with the formula in CKD patients of this age group. Figure 3 shows the correlation between these two serum Cr-based eGFR formulae in these patients. The eGFR using a quintic equation of body length (y) is shown as the eGFR using a linear equation of the body length (x) as follows: $y = 0.98x + 1.63$. In contrast, in CKD patients aged between 12 and 18 years old, the relation were shown as follows: $y = 1.06x + 6.56$.

Thus, the eGFR values derived from the two equations showed a good degree of accordance in Japanese CKD patients aged between 2 and 11 years old.

Comparison of performance of our new eGFR formula and the other eGFR formulae including the updated Schwartz formula

We used a diagnostic test design to compare our new polynominal eGFR formula, our simple linear formula previously reported in CEN [8], and 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; these are listed in Table 2. The new polynomial formula had significantly less bias than other eGFRs ($P < 0.001$). Accuracy was not significantly different between our simple linear formula and our polynomial formula, but significantly different between the two Schwartz's formulae and our polynomial formula. Root mean square error (RMSE) was lower for our new polynomial formula than for other eGFRs stratified by glomerular filtration rate measured by the inulin clearance method mGFR in all 131 subjects. In particular, Fig. 4 showed the RMSE between measured maximum inulin GFR and estimated GFR obtained using our polynomial formula in CKD patients aged between 2 and 16 years old was lower than the estimated GFR obtained using the updated Schwartz formula (17.2 vs. 18.3, respectively). The reason why we analyzed patients aged 2–16 years old was a limitation in updated Schwartz formula.

Discussion

The 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 estimated GFR [eGFR (ml/min/1.73 m^2) = k × body length (cm)/serum Cr level (mg/dl)] determined by the Jaffé method devised by Schwartz has been used clinically [1]. Recently, however, enzymatic methods have been used to measure Cr rather than the Jaffé method, so it is not possible to use the formula in this form. Therefore, it was necessary to reevaluate the value of the coefficient k in the formula. Recently, Zappitelli et al. [15] revised the Schwartz formula relating the eGFR to the serum creatinine level determined enzymatically and reported that the value of k in the Schwartz equation decreased from 0.55 to 0.47 for children and adolescent girls. Schwartz et al. reported the updated formula, the so-called "bedside" version, as eGFR = 0.413 × body length (cm)/serum Cr level (mg/dl) by the enzymatic method showing a 25 % reduction in value of k from the previous value of 0.55 generated from Jaffé-based serum Cr measurements and eGFR (ml/min/1.73 m^2) = 39.1 × [body length (m)/s − Cr (mg/dl)]$^{0.516}$ × [1.8/cystatin C (mg/l)]$^{0.294}$ × [30/BUN (mg/dl)]$^{0.169}$ × [1.099]^{male} × [body length (m)]/1.4]$^{0.188}$ by enzymatic Cr determination in children 1–16 years old [5]. This was defined in a population of American children with chronic kidney disease, enriched for those with obstructive uropathy. They concluded that the formula can be used in children 1–16 years old.

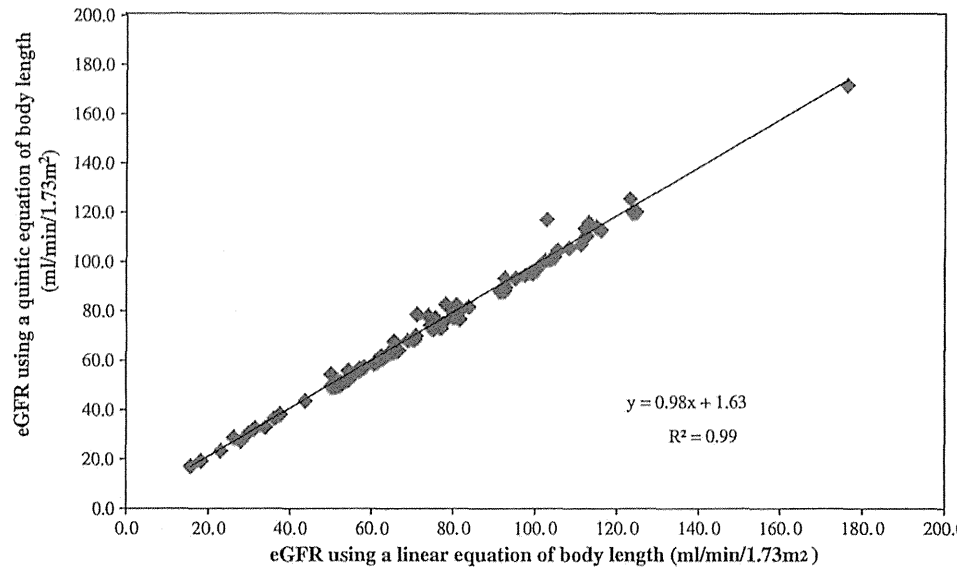

Fig. 3 Analysis of two eGFR equations in pediatric CKD patients aged between 2 and 11 years old. The two equations are eGFR using a linear and quintic equation of body length, respectively. The regression equation was $y = 0.976x + 1.63$. A significant positive correlation was observed in children with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

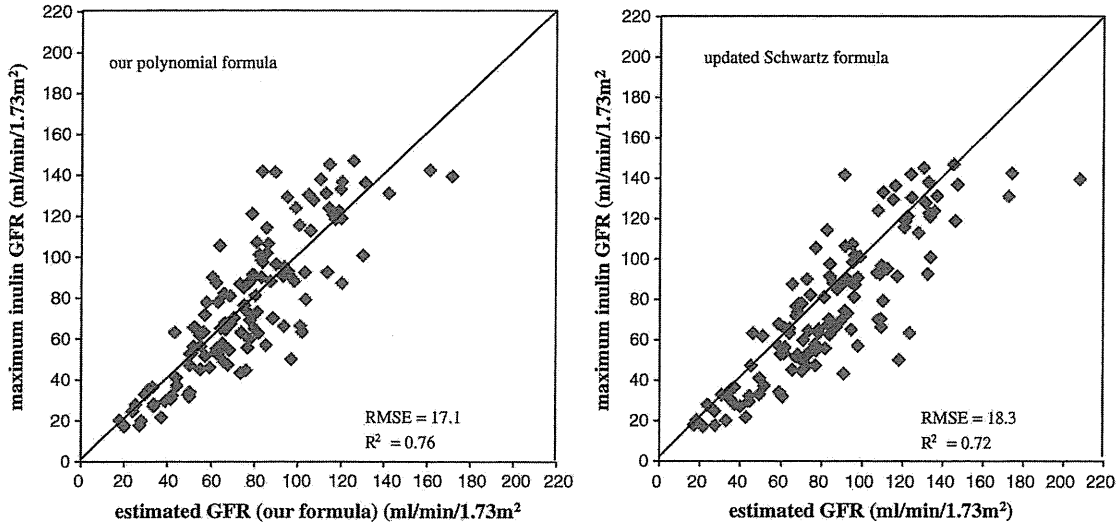

Fig. 4 Correlation between the estimated and measured maximum inulin GFR in CKD patients aged between 2 and 16 years old. *Left* Measured maximum inulin GFR versus the estimated GFR obtained using our polynomial formula. *Right* Measured maximum inulin GFR versus estimated GFR obtained using the updated 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 × 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.

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ORIGINAL ARTICLE

Satisfaction after the Malone antegrade continence enema procedure in patients with spina bifida

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Study design: Retrospective chart review.
Objective: To evaluate the clinical outcomes and factors influencing patient satisfaction with Malone antegrade continence enema (MACE) in patients with spina bifida.
Setting: Japan.
Methods: We performed retrospective analysis of 21 patients with spina bifida who underwent surgical creation of an MACE stoma. Clinical outcomes were evaluated by medical records, operative notes and mailed questionnaires. Patient satisfaction scores (SSs) were measured on a modified visual analog scale (VAS) from 1 to 10, and the factors influencing the SS were analyzed.
Results: A 100% return rate for the mailed questionnaires was achieved. All patients underwent *in situ* appendicocecostomy with cecal plication. There was only one complication that required surgical revision. Regarding fecal continence, the overall success rate was 90%. Although 4 patients (19%) had severe irrigation pain and 4 patients (19%) found the washout time intolerably long, 18 (85%) of them were satisfied with the MACE procedure. Age at operation, experience of retrograde colonic enema (RCE), experience of stomal leakage, increased comfort at school or workplace and increased comfort at sleepovers significantly influenced SSs.
Conclusion: MACE is a valuable option in achieving fecal continence in patients with spina bifida, with most patients being satisfied with the procedure. In our analysis, younger age at operation, previous experience of RCE, no stomal leakage and improvement of quality of life (enhanced comfort at school, workplace and sleepovers) significantly influenced the high satisfaction after MACE.
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Keywords: Malone antegrade continence enema; quality of life; patient satisfaction; fecal incontinence; spina bifida

INTRODUCTION

The Malone antegrade continence enema (MACE) procedure, which was first described in 1990 by Malone *et al.*,[1] has revolutionized the management and improved the quality of life (QOL) of patients with spina bifida who suffer from refractory constipation and fecal incontinence. However, it has been reported in a long-term follow-up study that a considerable number of patients have ceased the MACE procedure.[2] To select good candidates for the MACE procedure among patients with spina bifida, it is important to evaluate not only the status of the bowel, but also the overall patient satisfaction after the procedure. The aim of this study was to evaluate the factors that influence overall satisfaction after the MACE procedure in patients with spina bifida.

MATERIALS AND METHODS

An institutional review board-approved retrospective chart review was performed of patients with spina bifida who underwent the MACE procedure between June 2004 and February 2012, performed by a single surgeon at our institution. We collected demographic information on the patients and their families, surgical techniques and complications, from medical records and operative notes. The onymous questionnaire was mailed to all patients to evaluate the MACE procedure, its complications, clinical outcomes, comparison with prior retrograde colonic enema (RCE), influence on the QOL, impact on social confidence, satisfaction score (SS) and patients' recommendations to other patients. In addition, we asked the patients' caregivers to assess the changes in their daily life after the MACE procedure. In case of no response, the patient or caregiver was kindly reminded by telephone.

The patients' SS was evaluated on a modified visual analog scale (VAS) from 1 to 10 (Figure 1). In this scale, a higher score represents a higher level of satisfaction. To evaluate the factors influencing patient satisfaction, we analyzed the relationship between SS and 17 factors selected from the onymous questionnaire and demographic data. Data were analyzed using a two-tailed unpaired t test or Wilcoxon rank-sum test, as appropriate. For all statistical analyses, $P<0.05$ was considered as statistically significant. All statistical analysis was performed using JMP 9 (SAS Institute Inc., Cary, NC, USA).

RESULTS

During the study period, 22 patients with spina bifida underwent the MACE procedure at our institution. All patients suffered from intractable constipation and/or fecal incontinence before surgery. All the patients returned completed questionnaires (response rate, 100%). One female patient who refused to use MACE from the outset was excluded from the study. Hence, a total of 21 patients were included in this study. Their demographic data are shown in Table 1. There were 10 males (47%) and 11 females (52%), with a mean age of 19.5 years (range, 7.9–29.5 years). The median follow-up time was 75 months (range, 23–104 months). Clean intermittent catheterization of the bladder was performed in all patients and social urinary continence was achieved in 20 (95%) of them.

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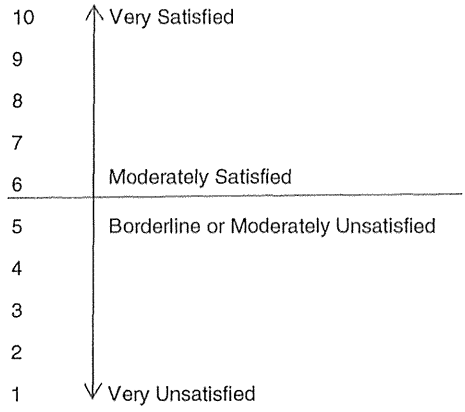

Figure 1 Modified VAS of SSs from 1 to 10 in the questionnaire. Score 5 means moderately unsatisfied and score 6 means moderately satisfied.

Table 1 Patient demographic data

Sex (n)	
Male	10
Female	11
Mean age (years)	19.5 (7.9–29.5)
Mean age at operation (years)	14.0 (4.0–23.0)
Median follow-up time (months)	75.0 (23.1–104.1)
Simultaneous urinary tract reconstruction (n)	
(+)	4
(−)	17
Experience of RCE (n)	
(+)	11
(−)	10
Ambulation (n)	
Ambulatory	14
Wheelchair bound	7
Primary diagnosis (n)	
Myelomeningocele	17
Lipomeningocele	4

Abbreviation: RCE, retrograde colonic enema.

In terms of the surgical procedure, all patients underwent *in situ* appendicocecostomy with cecal plication around the appendiceal base. Of the patients, 20 underwent umbilical anastomosis using the V-V appendicoplasty technique. Only one patient underwent skin anastomosis using VR skinplasty at the right lower quadrant of the abdomen due to the simultaneous performance of umbilical Mitrofanoff procedures.[3] The Malone stoma was created by laparotomy in all patients, and 17 patients underwent simultaneous urinary tract reconstruction, including bladder augmentation, bladder neck reconstruction, ureterocystostomy and Mitrofanoff procedures.

Assessment of surgical complications indicated that there were only two complications related to the MACE stoma. One patient with stomal mucosal prolapse underwent operative revision, while another one with minor stomal infection was treated with antibiotics. The remaining 19 patients had no postoperative complications requiring medical treatment. Of the 21 patients, 13 (62%) were completely independent following the MACE procedure. In only two patients, aged 14 and 16 years, the entire enema was performed by caregivers. The mean irrigation volume using tap water was 1150 ml (range, 700–2000 ml). The mean washout time was 60.4 min (range, 30–120 min). Four (19%) of the patients found the washout time intolerably long. Further, four of the patients (19%) felt intolerable irrigation pain.

The criteria for determination of fecal continence were based on the Malone criteria.[4] Full success (totally clean, experiencing only minor leakage of the washout at night), partial success (clean but with occasional major leakage) and failure (regular fecal incontinence episodes) were recognized in 11 (52.4%), 8 (38.1%) and 2 (9.5%) of the patients, respectively. However, all patients except one expressed definite improvement of fecal continence after MACE. Of the 21 patients, 1 male patient stopped use of the MACE 6 years after the operation due to prolonged washout time. However, after use of the MACE for such a long time, he became able to defecate by himself regularly.

Patient satisfaction

Of the 21 patients, 18 (85%) indicated SS of 6 or more. The mean SS was 7.8 (range, 5–10). Table 2 shows the relationship between SS and 17 factors, including demographics and several QOL data. Demographic data had no relationship with patient satisfaction, except for age at the time of the operation and experience of RCE. Figure 2 shows the SS of the patients in terms of age at the time of the operation. Comparison of the group that had surgery at a younger age ($\leqslant 10$ years) with those that had surgery at an older age (>10 years) indicated significantly higher SS in the younger age group. The SS of patients with RCE experience was significantly higher than patients without RCE experience ($P=0.02$). Duration of MACE usage had no effect on SS, there being no significant difference in SS between short usage ($\leqslant 5$ years) and long usage (>5 years) groups. Regarding the MACE procedure and clinical outcomes, independence in performing the procedure, status of fecal continence, severity of irrigation pain and tolerability of washout time did not significantly influence SS. However, patients with occasional stomal leakage reported significantly lower SS than patients without it ($P=0.02$). In the questions about QOL, there were no significant differences in SS between patients who wore and those who did not wear diapers during the daytime. Patients who felt enhanced comfort at school or the workplace and enhanced comfort at sleepovers after MACE indicated significantly higher SS. Of the 21 patients, 81% said they would recommend this procedure to other patients with spina bifida.

Answers from caregivers

Eighteen caregivers answered the questionnaire about the change in their daily life after MACE. Twelve of the eighteen (66%) caregivers reported that MACE relieved the burden of their daily life. All four caregivers of the patients who indicated the highest SS answered that MACE relieved their burden.

DISCUSSION

The MACE procedure, which was first described in 1990 by Malone *et al.*,[1] has revolutionized the management and improved the QOL of children with neuropathic bowel, refractory constipation and fecal incontinence.[5,6] In a systematic review of 24 studies, overall fecal continence was achieved in 93% of the patients.[7] However, it is difficult to compare success rates in patients at different centers and with different underlying diseases. Acceptance of the MACE procedure by patients with spina bifida at a special reference center may be different from that by children with anorectal malformations

Table 2 Influence of each of the 17 factors on satisfaction scores (SSs)

Question items	*N*	*Satisfaction score*	*P-value*
Gender			0.32
Male	10	8.3±1.6	
Female	11	7.5±1.7	
Age at operation (years)			<0.01
⩽10	6	9.5±0.6	
>10	15	7.2±1.5	
Follow-up period (years)			0.97
⩽5	9	7.7±1.9	
>5	12	7.9±1.6	
Ambulatory status			0.93
Ambulatory	14	7.8±1.7	
Wheelchair bound	7	7.9±1.7	
Independence after the procedure			0.54
Independent	13	8.0±1.6	
Not independent	8	7.5±1.8	
Simultaneous urinary tract reconstruction			0.32
(+)	4	8.7±0.5	
(−)	17	7.6±1.8	
Experience of RCE			0.02
(+)	11	8.6±1.4	
(−)	10	7.0±1.5	
Experience of minimal stomal leakage			0.02
(+)	5	6.4±0.8	
(−)	16	8.3±1.6	
Experience of painful catheterization			0.23
(+)	10	7.4±1.9	
(−)	11	8.3±1.4	
Length of washout time			0.15
Tolerable	17	8.1±1.5	
Intolerable	4	6.7±2.3	
Irrigation pain			0.65
Tolerable	17	8.0±1.7	
Intolerable	4	7.5±2.0	
Fecal continence			0.09
Full success	11	8.4±1.6	
Partial success or failure	10	7.2±1.6	
Improvement of constipation			0.34
(+)	16	8.0±1.6	
(−)	5	7.2±1.92	
Improvement of desire to defecate			0.97
(+)	14	7.8±1.8	
(−)	7	7.8±1.4	
Wearing diapers during the daytime			0.51
(+)	10	8.1±1.5	
(−)	11	7.6±1.9	
Enhanced comfort at school or workplace			0.03
(+)	16	8.4±1.3	
(−)	5	6.2±1.7	
Enhanced comfort at sleepovers			<0.01
(+)	10	9.1±0.8	
(−)	11	6.7±0.4	

Abbreviation: RCE, retrograde colonic enema.

at a clinic of pediatric surgery. In addition, despite the high success rates of the MACE procedure, Yardley *et al.*[2] reported in a long-term follow-up study that a considerable number of patients had ceased MACE procedures. On the other hand, they described that satisfaction rates were very high in patients who continued to use MACE over a

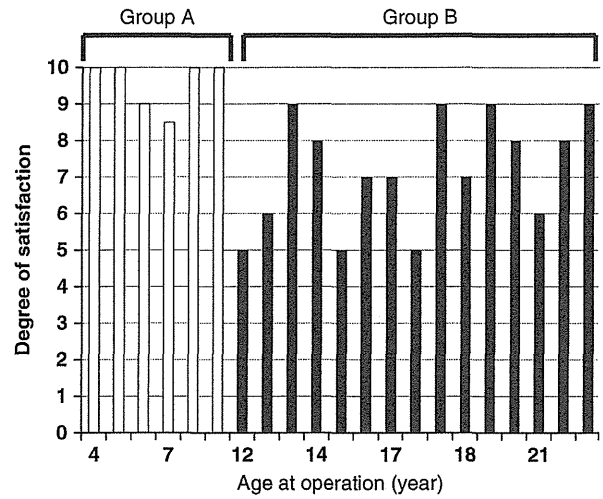

Figure 2 SSs of all patients in terms of age at operation.

long period of time. From this point on, to evaluate the MACE procedure, it is essential to investigate the success rate not only in terms of fecal continence, but also the degree of patient satisfaction after the procedure. If there are, indeed, several predictive factors influencing patient satisfaction after the MACE procedure, then knowledge of these factors will be useful to both physicians and patients when considering the indications of MACE.

Although this series was small, it included only spina bifida patients with intermittent catheterization. Furthermore, a 100% return rate for the mailed questionnaires and low dropout rate of MACE made this study quite adequate for evaluating SS following MACE. The reason for the low dropout rate (1 out of 21) is unknown. However, one possible explanation for this could be the continuing support of our nursing specialists at every patient visit.

The overall success rate in this study, which included partial success with occasional fecal leakage, was 90%, although only 52% achieved complete success. The mean age of patients at the time of evaluation in this study was higher than in previous studies (19.5 versus 10.7 years).[7] Vande Velde *et al.* described that the continent group of patients with spina bifida tended to be younger. In their study of MACE in patients with spina bifida, fecal continence was achieved in 6 of 7 children (86%) and 7 of 11 adults (64%).[8] In terms of surgical complications, our study showed very few complications. There were no serious complications, such as shunt infection, ileus and severe stomal stenosis requiring operative revision. Infection of the catheterizable stoma that developed in one patient was cured with medical management. Only one patient underwent stomal revision due to mucosal prolapse. Although occasional minimal stomal leakage and painful catheterization were recognized in a few patients, no patient needed additional surgery to fix these problems. The possible reason for this low complication rate was that we performed *in situ* appendicostomy with a cecal plication. With almost the same techniques, Herndon *et al.* reported that stomal revisions were required in 11 (8.7%) patients, which was lower than other previous reports.[7,9] They suggested that the reason for their low stomal revision rate was preservation of cecal blood supply at the base of the appendix, thereby limiting its dependence on an isolated appendiceal mesentery.

In terms of overall patient satisfaction, our study showed a satisfaction rate (SS⩾6) of 85% with a mean SS of 7.8 (range, 5–10).

Hoekstra *et al.*[6] reported relatively similar results of SS on almost the same scale from 1 to 10 in children with intractable defecation disorders. In their study, 86% of the patients were satisfied, with a median score of 8 (range, 6–10). In this study, we analyzed the factors influencing patient satisfaction. To our knowledge, there has been no study that determined which patient variables have an impact on patient satisfaction after the MACE procedure, particularly in patients with spina bifida. Yerkes *et al.*[5] used satisfaction and QOL questions based on a 5-point Likert scale in 65 patients (including 57 with myelodysplasia), and found that responses for overall satisfaction were very satisfied, satisfied and very dissatisfied in 89, 9 and 1.5%, respectively.[5] They opined that it was not possible to stratify patients to determine the factors influencing patient satisfaction due to the large percentage of positive responses. To make a detailed analysis of patient satisfaction, we used a modified VAS from 1 to 10 to assess SS, instead of the 5-point Likert scale. Although measurement of patient satisfaction with VAS has not received wide acceptance particularly in children <10 years of age, it has previously been used in other subjects and has been shown to be valid in previous reports.[10,11] The overall satisfaction rate in this study was 85.7%, however, only four patients (19%) scored 10.

Many questions about the MACE procedure and QOL after the procedure were asked in this cohort, in an attempt to define the variables predicting patient satisfaction. In our analysis, there were five factors, including age at operation, experience of RCE, experience of minimal stomal leakage, enhanced comfort at school or workplace and enhanced comfort at sleepovers, that significantly influenced SS. When divided into younger (10 years and younger) and older age (11 years and older) groups, patients with MACE introduction at a younger age showed significantly higher SS, as demonstrated by the fact that four of the six patients in the younger age group scored 10 on the VAS in this study. Although the questionnaires were mailed to the patient and the present age of most patients was above 10 years, we assume that a parent completed the questionnaire in many of the younger age group patients. Therefore, their responses may reflect the opinions of the parent rather than the patient. In fact, the caregivers of all the four younger age patients who scored 10 on SS answered that MACE relieved their burden. On the other hand, older age group patients, particularly adolescents, tended not to be highly satisfied with the procedure.

In our cohort, previous experience of RCE was significantly related to the SS. This finding definitely supports stepwise and individually tailored bowel management programs by a multidisciplinary team starting in childhood.[12] It can be easily imagined that patients and their caregivers would appreciate the ease of MACE procedures and its high success rate compared with their previous bowel management strategy, particularly RCE. Patients who have not previously experienced problematic bowel management strategies seem to be not highly satisfied with MACE, regardless of their bowel condition. In our study, the perfection of continence was not significantly related to SS. However, the occasional experience of even minimal stomal leakage significantly decreased SS. This indicates that patients strongly fear even a small stain on their shirts.

In our previous study, procedure independence was significantly better in the MACE group compared with the RCE group in children with spina bifida.[13] However, the level of independence was not significantly related to SS. Furthermore, SS had no relation to whether or not the patients wore diapers during the daytime. These findings may reflect the overall limit of independence, complete urinary continence and fecal continence in these patients. Finally, significantly higher SS was recognized in patients who felt enhanced comfort at school, their workplace and at sleepovers after MACE. Thus, we should not only be concerned about the patients' bowel condition, but also strongly encourage and support patients in their daily life after MACE.

The main limitations of this study include its retrospective design, using a non-validated questionnaire, small size of the cohort, and the use of VAS which is not a validated tool for patient satisfaction in children <10 years of age. Besides these, our study results are also limited by the fact that the majority of our patients underwent simultaneous urinary tract reconstruction. Although there was no significant difference in SS on the basis of status of simultaneous urinary tract reconstruction, and it was stressed that the focus of the questionnaire was the MACE procedure, patients' SS may have been influenced by their urinary tract condition after surgery. In addition, assessment of bowel condition was based on the self or caregiver reported outcomes, without physiologic evaluation.

Conclusions

In our analysis, younger age at operation, previous experience of RCE, no stomal leakage and improved QOL (greater comfort at school, workplace and sleepovers) significantly contributed to the high satisfaction after the MACE procedure in patients with spina bifida.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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