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Evaluation of Renal Function in Children with Congenital Scoliosis and Congenital Anomalies of the Kidney and Urinary Tract

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Background: The aim of this study was to compare renal function in children with congenital scoliosis and congenital anomalies of the kidney and urinary tract, with healthy children.

Material/Methods: Biochemical tests were performed before surgery (pre-therapy) and after surgery (post-therapy) in 16 children with congenital scoliosis and congenital anomalies of the kidney and urinary tract. Thirty-two healthy children were matched for age, sex, and weight (healthy controls). General renal function tests included serum electrolytes, creatinine, urea, cystatin C, and estimated glomerular filtration rate (eGFR). Tests for early renal changes included N-acetyl-beta-D-glucosaminidase (NAG), urine microalbumin, serum transferrin, immunoglobulin G (IgG), urinary alpha-1-microglobulin (A1M), and beta-2-microglobulin (B2M).

Results: Sixteen patients with congenital anomalies of the kidney and urinary tract included eight boys (mean age, 11.38±2.00 years) and eight girls (mean age, 11.00±2.78 years). There were no significant differences in renal function between the pre-therapy and post-therapy groups ($P>0.05$), or between the three groups (pre-therapy, post-therapy, and healthy controls). In the pre-therapy group, there were significant differences in IgG, A1M, NAG, and serum phosphate levels between boys and girls, urine microalbumin was significantly increased in girls, but not boys ($P<0.05$). There were no significant differences between the pre-therapy group and post-therapy group ($P>0.05$).

Conclusions: Routine tests of renal function were normal in children with congenital scoliosis and congenital anomalies of the kidney and urinary tract, but early changes in renal function occurred before surgical treatment, indicating long-term follow-up of renal function is recommended.

MeSH Keywords: Kidney Function Tests • Pediatrics • Scoliosis • Urogenital Abnormalities

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Background

Congenital scoliosis is a form of spinal curvature that is caused by the presence of an underlying congenital vertebral malformation and is clinically defined as a lateral curvature of the spine exceeding 10 degrees [1]. In between 30–60% of cases of congenital scoliosis, there are concomitant congenital deformities that may involve the nervous system, the cardiovascular system, the musculoskeletal system, the genitourinary system and other systems [2], especially the genitourinary system, respiratory system and cardiovascular system, which have a common embryological origin from the mesoderm [3,4]. Congenital anomalies of the kidney and urinary tract collectively is a collective term that refers to a diverse group of structural malformations involving the kidneys, renal collecting system, bladder, or urethra, which occur at a frequency of 1 in 500 live births [5,6]. Congenital anomalies of the kidney and urinary tract are frequently associated with congenital scoliosis [7–10].

Previously published studies in pediatric orthopedic surgery have shown [7–10] that congenital anomalies of the kidney and urinary tract are among the most frequent congenital abnormalities associated with congenital scoliosis, and the incidence of this association ranges from between 11–37% [7–10]. Also, most patients with congenital anomalies of the kidney and urinary tract often have no clinical symptoms and may be assumed not to need surgical or other treatment intervention [7–10]. Previously published studies on congenital anomalies of the kidney and urinary tract have demonstrated the long-term clinical risks, involving impairment in renal function [4,11–14]. Congenital anomalies of the kidney and urinary tract are a leading cause of chronic kidney disease (CKD), accounting for between 30~60% of children with end-stage renal disease, who may require treatment with renal transplantation in childhood [11,12].

Furthermore, renal transplantation for end-stage renal disease occurs earlier in patients with congenital anomalies of the kidney and urinary tract, compared with patients without these congenital abnormalities (31 years *vs.* 61 years). Most cases of congenital anomalies of the kidney and urinary tract are not detected until clinical symptoms develop, and for some cases, they are diagnosed in patients with end-stage renal disease and require renal dialysis or renal transplantation.

Previously published studies have mainly focused on the morphology, epidemiology or pathogenesis of congenital anomalies of the kidney and urinary tract in children with congenital scoliosis. Few previous studies have evaluated renal function in these cases. Therefore, the aim of this study was to compare renal function in 16 children with congenital scoliosis and congenital anomalies of the kidney and urinary tract, with 32 healthy children.

Material and Methods

Study population

Sixteen pediatric inpatients, with a definitive diagnosis of congenital scoliosis with congenital anomalies of the kidney and urinary tract, who were treated in the Department of Orthopaedics, and 32 age-matched, sex-matched, and weight-matched healthy control children were selected from the Health Examination Center of the Second Affiliated Hospital of Xi'an Jiaotong University, between from January 2015 to October 2017, were enrolled into the study.

Scoliosis was defined as curvature deformity of the spine that is seen in the coronal plane, which is usually accompanied by a variable degree of rotation of the spinal column, ≥10° of curvature (the Cobb angle). The location of congenital scoliosis was defined by the apical vertebra (the one that most deviated and rotated from midline). Three types of congenital scoliosis were diagnosed in the patients in this study, according to the classification described by Hedequist and Emans, including I: failure of vertebral formation; II: failure of vertebral segmentation; and III: a mixed deformity, or combination of I, and II [15].

The spectrum of congenital anomalies of the kidney and urinary tract included one or more of the following structural malformations: kidney agenesis, congenital multicystic kidneys, kidney dysplasia, kidney hypoplasia, ectopic kidney, horseshoe kidney, vesicoureteral reflux, mega-ureter, ectopic ureter, duplex renal collecting system, posterior urethral valves, ureteropelvic junction obstruction, and hypospadias. Subjects with liver disease, cardiovascular disease, nephropathy, or urinary tract infection, and individuals who were being treated with any drug therapy were excluded.

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University. Written informed consent was provided by the parents or a legal guardian of the patients in the study.

Laboratory investigations of blood and urine

A comprehensive physical examination was performed on all study participants. Venous blood samples and midstream urine samples were obtained from all patients following an overnight fast before surgery (pre-therapy) and on day 14 or longer after surgery (post-therapy) and during the hospital stay. The samples were analyzed in a routine clinical biochemistry laboratory. Liver function tests, general renal function tests, and analysis of electrolytes were undertaken using an automatic biochemical analyzer, the Olympus AU2700 (Olympus, Japan). Urinalysis was performed using a urine sediment analysis instrument the Sysmex UF-1000i Automated Urine Particle Analyzer (Sysmex Corporation, Kobe, Japan).

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Urinary biomarkers of early impairment of renal function, including urine microalbumin, serum transferrin, immunoglobulin G (IgG), urinary alpha-1-microglobulin (A1M), and beta-2-microglobulin (B2M) were measured using the immune scatter turbidity method, and N-acetyl-beta-D-glucosaminidase (NAG) was measured by colorimetry. For each patient, these biomarkers were measured in triplicate before surgery (pre-therapy) and in triplicate ≥14 days after surgery (post-therapy), respectively. All clinical laboratory tests were carried out at the Central Laboratory of the Second Affiliated Hospital, Xi'an Jiaotong University.

Imaging studies

Spinal and abdominal imaging were performed using ultrasonography, X-ray radiography, computed tomography (CT) and magnetic resonance imaging (MRI) scans were performed in all patients to obtain a comprehensive diagnosis as well as to provide a treatment strategy. Ultrasonography was the main screening method used to identify other organ deformities, including of the heart, kidney, and ureter.

Data collection

The clinical, biochemical, and imaging characteristics of the 16 children with congenital scoliosis and congenital anomalies of the kidney and urinary tract, and the 32 healthy children were matched for age, sex, and weight (healthy controls) including the detailed parameters of renal function, hepatic function, and cardiac function, were recorded.

Serum creatinine, urea, cystatin C, and estimated glomerular filtration rate (eGFR) were used to assess general renal function. Tests for early renal changes included N-acetyl-beta-D-glucosaminidase (NAG), urine microalbumin, serum transferrin, immunoglobulin G (IgG), urinary alpha-1-microglobulin (A1M), and beta-2-microglobulin (B2M). Serum electrolytes, including serum sodium (Na^+), potassium (K^+), chloride (Cl^-), bicarbonate (HCO_3^-), serum calcium (Ca^{2+}) and serum phosphate, were measured to evaluate electrolyte disturbances. The left ventricular ejection fractions (LVEF) was used to determine cardiac function.

Statistical analysis

Statistical analysis was performed using SPSS version 23.0 software (SPSS, Inc., Chicago, IL, USA). The average of measurements performed in triplicate in each patient and healthy individual were recorded in all study participants, before surgery (pre-therapy), and after surgery (post-therapy) and in 32 healthy children who were matched for age, sex, and weight (healthy controls). Normally distributed variables are presented as the mean ± standard deviation (SD), and non-normally distributed variables were expressed as the median and interquartile range. Categorical variables were expressed as the number of patients and the percentage. Comparisons of baseline characteristics were performed using t-tests. The chi-squared (χ^2) test was used to test the statistical significance between the two groups according to sex (boys and girls). Comparisons for all biomarkers were performed using one-way analysis of variance (ANOVA) if normally distributed, or the Kruskal-Wallis H test. The Student-Newman-Keuls (SNK) method, a stepwise multiple comparisons procedure, was used to identify sample means that were significantly different from each other, or the Wilcoxon rank-sum test was used to perform multiple comparisons among the three groups studied if there was a significant difference between the three groups (pre-therapy, post-therapy, and healthy groups). Correlations were determined with Spearman's test. A P-value of $P<0.05$ was considered to be statistically significant.

Results

Inclusion characteristics of study participants

Sixteen patients with congenital anomalies of the kidney and urinary tract, included eight boys (mean age, 11.38±2.00 years) and eight girls (mean age, 11.00±2.78 years), were chosen from 124 patients with congenital scoliosis, who met the study criteria.

Thirty-two healthy children were matched for age, sex, and weight (healthy controls). Ten patients with congenital anomalies of the kidney and urinary tract (four with a solitary kidney, two with an ectopic kidney, two with hypospadias, one with a horseshoe kidney, and one with pelvi-ureteric junction obstruction) were excluded as they had undergone previous surgery or also had cardiac defects, obstructive uropathy, or urinary tract infection. During patient selection and initial review of 124 patients, the concomitant incidence of congenital anomalies of the kidney and urinary tract in patients with congenital scoliosis was 20.96% (26/124). The characteristics of 16 patients included in this study and concomitant deformities are shown in Table 1.

Of the 16 patients with congenital anomalies of the kidney and urinary tract, five patients had a solitary kidney. Three patients had hypospadias and had received surgical treatment at 10, and 12 months of age. Three patients had an ectopic kidney. Two patients had duplicate ureters (both a Y-shaped ureter, without an ectopic ureteral orifice). One patient had a horseshoe kidney. One patient had a polycystic kidney, and one patient had pelvi-ureteric junction obstruction with mild hydronephrosis and had received surgery at 3 years-of-age.

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Table 1. Detailed characteristics of 16 CS inpatients with CAKUT.

No.	Sex F/M	CS T/TL	Age (year)	Type of scoliosis	Cobb's angle (°)	Concomitant malformations	CAKUT
1	M	T	13	I	85	Syringomyelus; Spina Bifida Occulta	Solitary kidney
2	F	TL	11	III	78	Diplomyelia; Spina Bifida Occulta	
3	F	TL	9	II	59	None	
4	M	TL	12	I	78	Diplomyelia; Spina Bifida Occulta	
5	M	T	14	I	57	Diplomyelia; Spina Bifida Occulta; Chiari Malformation	
6*	M	T	11	I	65	Diplomyelia; cryptorchidism	Hypospadias
7*	M	T	11	III	76	Diplomyelia; Spina Bifida Occulta	
8*	M	T	8	I	67	Tethered Cord Syndrome; intradural lipomas	
9	M	TL	12	I	67	Diplomyelia; Tethered Cord Syndrome	Ectopic kidney
10	F	TL	7	I	87	diastematomyelia; Spina Bifida Occulta	
11	M	T	9	II	90	Spina Bifida Occulta	
12	F	TL	12	I	87	None	Duplicate ureters
13	F	T	15	II	81	Diplomyelia; Tethered Cord Syndrome	
14	F	T	8	I	94	Diplomyelia; Congenital uterine agenesis; Congenital colpatresia	Horseshoe kidney
15	F	TL	13	II	90	None	Polycystic kidney
16*	F	TL	13	I	69	None	PUJO

CS – congenital scoliosis; F – Female; M – Male; TL – thoracolumbar scoliosis; T – thoracic scoliosis; I – failure of vertebral formation; II – failure of vertebral segmentation; III – mixed deformity, a combination of I and II; PUJO – pelviureteric junction obstruction. 6*, 7*, 8*, and 16* accepted surgical operation at the age of 10, 12, and 12 months old and 3 years old, respectively.

All children included in the study had no symptoms of urinary tract infection or abnormal renal function. Patient factors including sex, age, weight, albumin, LVEF, hematocrit, hemoglobin, urine specific gravity, and blood uric acid were not significantly different between the two groups. Liver function tests, cardiac ultrasonography, and full abdomen ultrasound showed that all patients had no liver disease or structural or functional cardiovascular disease. The detailed baseline characteristics of 16 children with congenital scoliosis and congenital anomalies of the kidney and urinary tract and 32 healthy individuals are presented in Table 2.

Routine serum biomarkers of renal function

The serum levels of serum electrolytes, creatinine, urea, cystatin C, and estimated glomerular filtration rate (eGFR) in all subjects were within normal reference ranges. There were no significant differences in these routine biomarkers of renal function between the three groups, in boys or girls (P>0.05) (Figures 1, 2).

Urinary biomarkers of early renal function

Results for the tests for early renal changes included N-acetyl-beta-D-glucosaminidase (NAG), urine microalbumin, serum

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Table 2. Detailed baseline characteristics of patients and healthy individuals.

Characteristics	CAKUT group	Healthy group	P value
Age, years			
Female	11.00±2.78	11.13±2.50	0.912
Male	11.38±2.00	11.69±1.82	0.704
Sex, n			
Female	8	16	1.000
Male	8	16	1.000
Weight, kg			
Female	37.40±12.30	38.40±10.60	0.837
Male	42.55±8.18	42.91±7.70	0.918
Albumin, g/L			
Female	43.41±4.28	43.83±3.03	0.784
Male	44.66±2.48	44.23±3.38	0.753
LVEF,%			
Female	60.25±2.31	60.06±1.69	0.823
Male	59.63±1.60	60.50±1.15	0.138
Haematocrit,%			
Female	38.69±2.51	38.87±1.76	0.833
Male	39.49±1.35	39.04±2.21	0.609
Haemoglobin, g/L			
Female	128.00±8.35	130.25±6.04	0.457
Male	133.00±4.24	135.44±8.28	0.445
Urine specific gravity			
Female	1.024±0.008	1.021±0.008	0.454
Male	1.024±0.007	1.022±0.008	0.659
Blood uric acid, umol/L			
Female	263.13±42.32	261.81±44.60	0.946
Male	269.38±62.47	267.38±49.37	0.932

CAKUT – congenital anomalies of the kidney and urinary tract; LVEF – left ventricular ejection fractions.

transferrin, immunoglobulin G (IgG), urinary alpha-1-microglobulin (A1M), and beta-2-microglobulin (B2M). The serum levels of IgG, A1M, and NAG were significantly increased in patients with congenital scoliosis and congenital anomalies of the kidney and urinary tract compared with healthy individuals, for both boys and girls (P<0.05), but there were no significant differences in the serum levels of transferrin and B2M (Figures 3, 4). The concentration of urine microalbumin in girls was significantly greater compared with healthy individuals (P<0.05) (Figure 4), but there were no significant differences in boys. Also, no statistical significance was found in any variables before or after orthopedic surgical treatment in both boys and girls (P>0.05) (Figures 3, 4).

Serum electrolytes

Analysis of serum electrolytes showed that there were no significant differences in the concentrations of Na^+, K^+, Cl^-, HCO_3^-, and Ca^{2+} between the three groups, for boys and girls (P>0.05). However, the serum phosphate concentration was significantly different (P<0.05) between boys and girls between the three groups (Figures 5, 6). The serum phosphate concentration in

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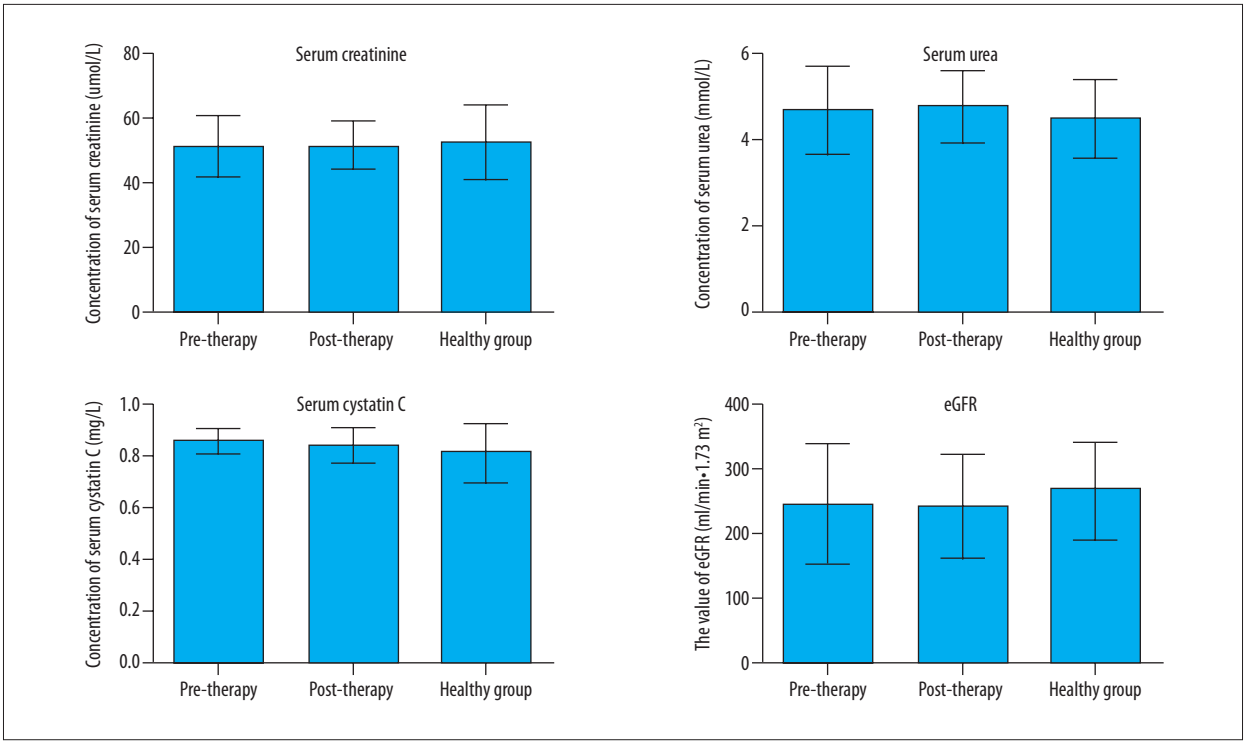

Figure 1. The levels of serum creatinine, urea, cystatin C, and estimated glomerular filtration rate (eGFR) in venous blood in boys. The results are presented as the mean ± standard deviation (SD). The levels of each parameter and estimated glomerular filtration rate (eGFR) are compared between the three study groups.

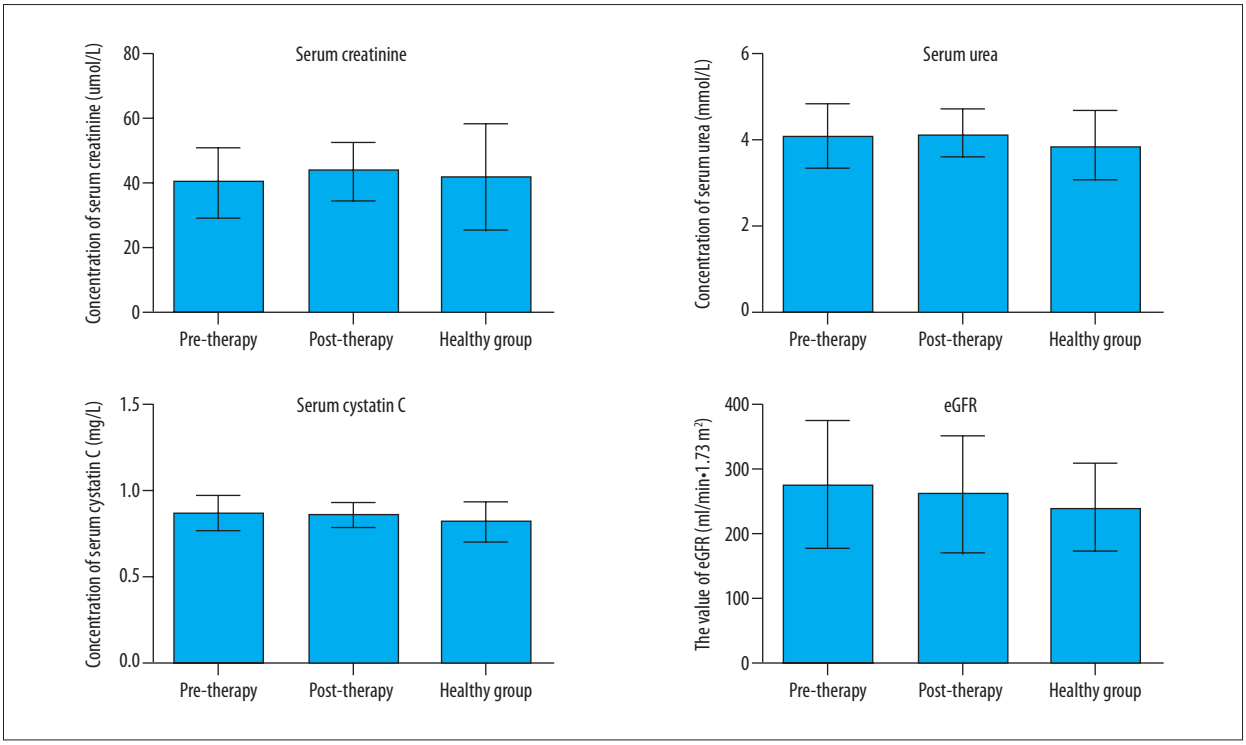

Figure 2. The levels of serum creatinine, urea, cystatin C and estimated glomerular filtration rate (eGFR) in venous blood in girls. The results are shown as the mean ± standard deviation (SD). The levels of each parameter and estimated glomerular filtration rate (eGFR) are compared between the three groups.

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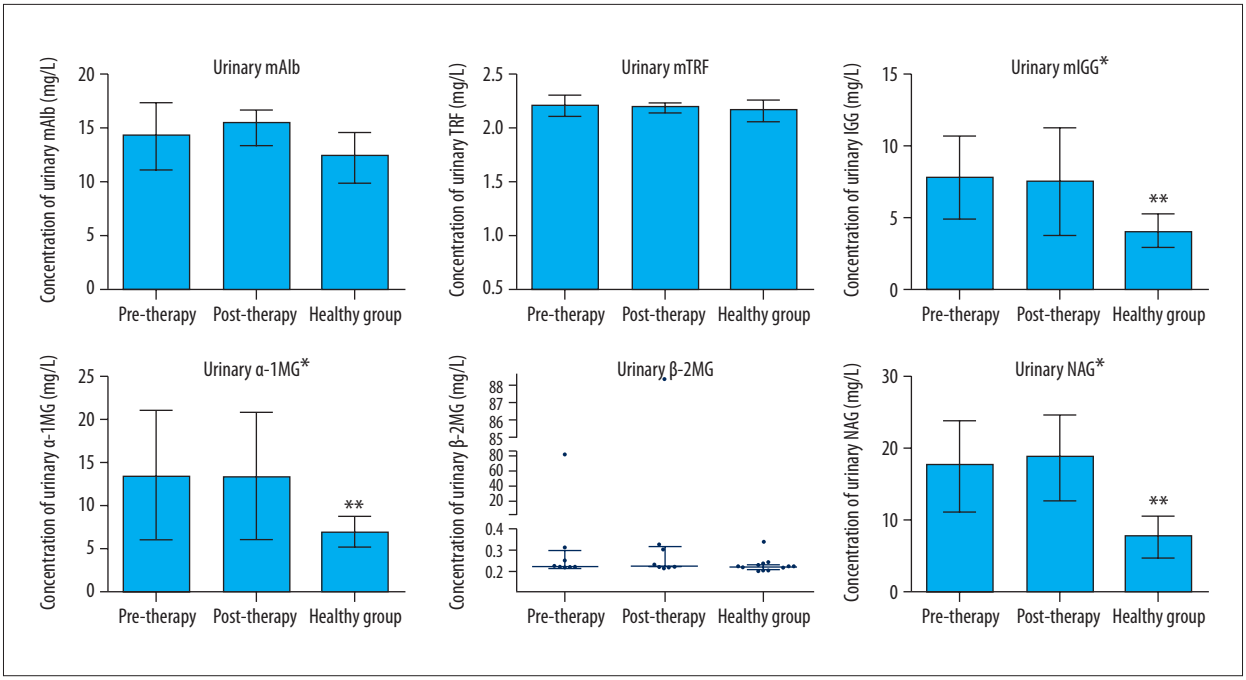

Figure 3. The concentration of urinary microalbumin, transferrin, IgG, alpha-1-microglobulin (A1M), beta-2-microglobulin (B2M), and N-acetyl-beta-D-glucosaminidase (NAG) in boys. The results are shown as the mean ± standard deviation (SD), or median and interquartile range for beta-2-microglobulin (B2M). The concentrations of each variable are compared between the three groups. * P<0.05 between the three groups; ** P<0.05 healthy group *vs.* pre-therapy group or post-therapy group.

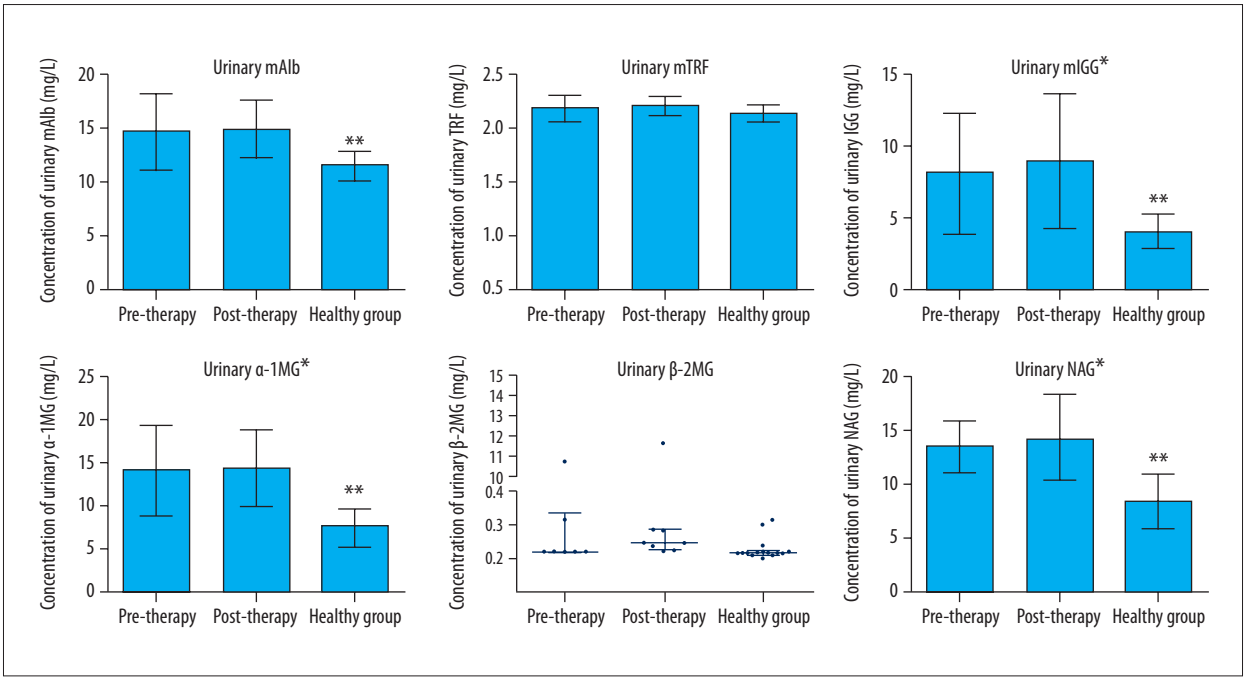

Figure 4. The concentration of urinary microalbumin, transferrin, IgG, alpha-1-microglobulin (A1M), beta-2-microglobulin (B2M), and N-acetyl-beta-D-glucosaminidase (NAG) in girls. The results are shown as the mean ± standard deviation (SD), or median and interquartile range for beta-2-microglobulin (B2M). The concentrations of each variable are compared between the three groups. * P<0.05 between the three groups; ** P<0.05 healthy group *vs.* pre-therapy group or post-therapy group.

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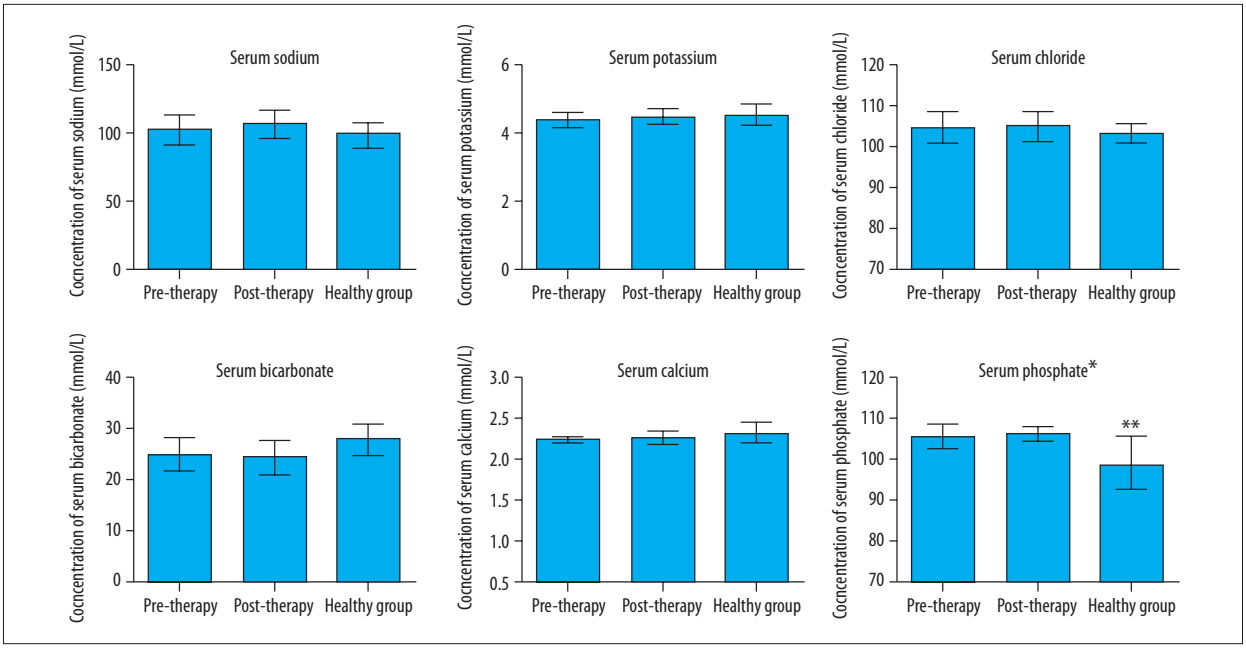

Figure 5. The concentration of serum sodium (Na^+), potassium (K^+), chloride (Cl^-), bicarbonate (HCO_3^-), calcium (Ca^{2+}), and phosphate in boys. The results are presented as the mean ± standard deviation (SD). Comparisons are performed between the three groups. The Student-Newman-Keuls (SNK) method, a stepwise multiple comparisons procedure, was used to identify sample means that were significantly different from each other, between the post-therapy group, the healthy group, and the pre-therapy group. * P<0.05 between the three groups; ** P<0.05 between the healthy group *vs.* the pre-therapy group or the post-therapy group.

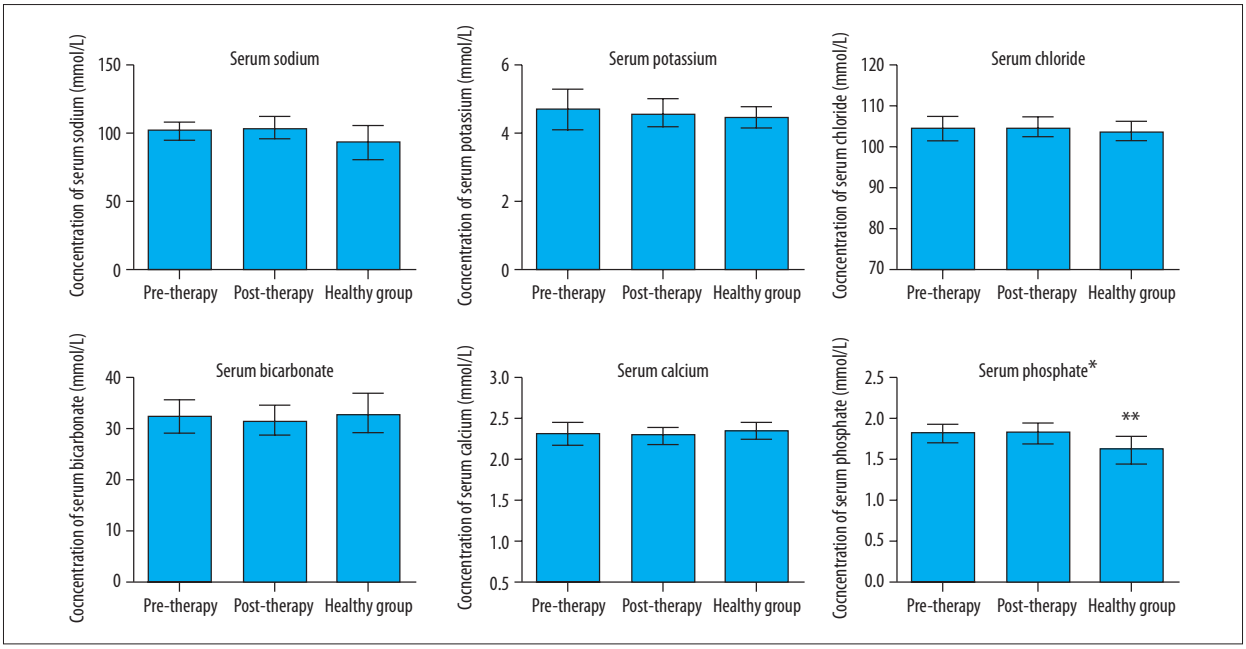

Figure 6. The concentration of serum sodium (Na^+), potassium (K^+), chloride (Cl^-), bicarbonate (HCO_3^-), calcium (Ca^{2+}) and phosphate in girls. The results are presented as the mean ± standard deviation (SD). Concentrations of each variable are compared among the three groups. The Student-Newman-Keuls (SNK) method, a stepwise multiple comparisons procedure, was used to identify sample means that were significantly different from each other, between the post-therapy group, the healthy group, and pre-therapy group. * P<0.05 between the three groups; ** P<0.05 between the healthy group *vs.* the pre-therapy group or the post-therapy group.

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Table 3. Summarized data for CS patients with CAKUT from previous studies.

Studies	Observation			CAKUT spectrum						
	Patients (n)	CAKUT (n)	Percentage (%)	Solitary kidney (n)	Ectopic kidney (n)	Duplicate ureters (n)	Horseshoe kidney (n)	Urethra deformity (n)	Renal hypoplasia (n)	Others
MacEwen [7]	231	42	18.0	15	6	9	1	10	1	0
Drvaric [8]	100	37	37.0	11	5	5	2	8	6#	
Beals [16]	218	29	13.3	17#		0	0	11	1	0
Rai [9]	202	54	26.7	24	9	9	5	9	6#	
Basu [17]	126	25	20.6	3	2	0	3	12	5	0
Shen [10]	226	19	8.4	4	6	0	1	4	4	0
Total*	1103	206,177*	18.7	57*	28*	23	12	54	11*	0

Unclear classification; * data with unclear classification were not included.

patients with congenital scoliosis and congenital anomalies of the kidney and urinary tract was significantly greater compared with healthy individuals (P<0.05). Also, there was no significant difference in the serum phosphate concentration between the pre-therapy and post-therapy groups (Figures 5, 6).

Discussion

There have been several previously published studies that have focused on the morphological and epidemiological diagnosis of congenital anomalies of the kidney and urinary tract, but there have been few studies on the concomitant incidence of congenital scoliosis. Therefore, the aim of this study was to compare renal function in children with congenital scoliosis and congenital anomalies of the kidney and urinary tract, with healthy children.

The findings of the present study, from a single center, showed that the incidence of the occurrence of both conditions of congenital scoliosis with congenital urological abnormalities was 20.96% (26/124), with the most frequent form or congenital renal anomaly being unilateral renal agenesis in 34.62% (9/26). The prevalence and incidence of these associations are supported by data from previously published studies, which have reported a concomitant incidence of 18.7% (206/1103) and a reported frequency of unilateral renal agenesis of 32.2% (57/177). (Table 3) [7–10,16,17].

The present study included an analysis of routine serum and urinary biomarkers of renal function and was the first study to evaluate renal function following the diagnosis of congenital anomalies of the kidney and urinary tract in children with congenital scoliosis. The 'gold standard' or routine laboratory techniques for accurate measurement of renal function in patients are infusion techniques that most commonly include ^{51}Cr-ethylenediaminetetraacetic acid (EDTA) or ^{99}m-Tc-diethylenetriaminepentaacetic acid (DTPA) clearance techniques [18]. However, these infusion techniques are invasive, laborious, and time-consuming, and may not be applicable for use in pediatric patients. Therefore, measurements of serum creatinine, urea, cystatin C, and estimated glomerular filtration rate (eGFR) are commonly used and are important methods for use in the evaluation of renal function in pediatric patients, with serum creatinine being the most widely used and important biomarker in the evaluation of renal function [18].

Serum cystatin C is a more precise and specific biomarker of renal function, as it reflects the glomerular filtration rate (GFR), and is considered to be superior to measurements of serum creatinine [19]. The estimated glomerular filtration rate (eGFR) is now accepted to be the best overall index of renal function [20]. Endogenous production of these biomarkers of renal function, cystatin C and eGFR, is constant in healthy individuals, and their serum and plasma levels represent glomerular filtration function, and these biomarkers increase with decreasing renal function [21]. However, in children, cystatin C and eGFR been shown to vary with age, gender, and weight. Therefore, in the present study, age-matched, sex-matched, and weight-matched healthy children were included to balance any underlying confounding factors.

The results of the present study showed that the serum concentrations of creatinine, urea, cystatin C, and eGFR in children with congenital scoliosis and congenital anomalies of the kidney and urinary tract were not significantly different from those in healthy individuals, both in boys and girls (Figures 1, 2), which indicated no impairment in renal function. Also, all patients

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included in this study initially had insufficient indications for surgical or medical intervention. These findings might explain why most patients with congenital anomalies of the kidney and urinary tract are untreated when initially admitted to hospital.

Recently, there have been major advances in the identification of biomarkers of early changes in renal function, and in studies on the molecular pathology of congenital anomalies of the kidney and urinary tract. New biomarkers of early changes of renal function, which might be investigated further in future studies, include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin (IL)-18, cystatin C, alpha-1-microglobulin (A1M), fetuin-A, Gro-alpha, beta-2-microglobulin (B2M), serum transferrin, IgG, N-acetyl-beta-D-glucosaminidase (NAG) [11,22]. KIM-1 has been shown to be a more sensitive and specific biomarker of early changes in renal function when compared with NAG [23]. However, some of these novel biomarkers, including KIM-1, NGAL and IL-18, have not been widely used in clinical practice. Therefore, in the present study, measurements of urine microalbumin, serum transferrin, and IgG were used as the biomarkers of early renal glomerular injury, and A1M, B2M, and NAG were used as biomarkers of early renal tubular damage to determine early changes in renal function.

The results of this study showed that there were significant differences in the concentration of IgG, A1M, and NAG between patients and healthy individuals in both boys and girls (Figures 3, 4). Also, the concentration of urine microalbumin was significantly increased in female patients compared with healthy girls, but not in boys. Different types of congenital anomalies of the kidney and urinary tract in girls may be the reason for this finding. The results of this study supported that early changes in renal function in children with congenital scoliosis and congenital anomalies of the kidney and urinary tract, especially renal tubular function, can occur.

The serum concentrations of phosphate in patients with congenital scoliosis and congenital anomalies of the kidney and urinary tract were significantly increased compared with healthy individuals, for both boys and girls. Previous studies have shown that the detection of abnormal phosphate metabolism was one of the hallmarks of chronic kidney disease (CKD), resulting in increased cardiovascular morbidity and mortality [24–27]. Also, a high serum phosphate level is a risk factor for poor clinical prognosis in patients with CKD. In this study, there was a positive association between the serum phosphate levels and the progression of kidney disease, which might be explained by the fact that increased phosphate concentrations can result in renal parenchymal calcification and proteinuria, and can induce a phenotypic change in vascular smooth muscle cells, which might promote arterial or arteriorenal calcification. However, in the present study, there was no linear relationship between serum phosphate levels and the concentrations of renal biomarkers. Therefore, the relationship between the serum phosphate level and severity of early renal functional impairment in patients with congenital scoliosis and congenital anomalies of the kidney and urinary tract requires further research.

In this study, a comparison of biomarkers of early changes in renal function and routinely used diagnostic biomarkers of general changes in renal function confirmed that serum creatinine, urea, cystatin C, and eGFR were biomarkers that evaluated renal function or glomerular filtration function. However, glomerular filtration function has a powerful compensative capacity and remains normal unless this compensative capacity is severely reduced in patients with moderate or severe renal functional damage. Also, serum creatinine is usually elevated under conditions of moderate to severe impairment of renal function, such as a 50% glomerular loss, but cystatin C might not be an accurate marker of mild renal impairment. Also, it is more likely that early renal function injury results from renal tubular damage rather than renal glomerular injury. Therefore, for this study, it was assumed that measurement of urine microalbumin, serum transferrin, IgG, A1M, B2M, NAG, and especially, the biomarkers of renal tubular damage, A1M, B2M, and NAG, were superior biomarkers to detect early changes of impaired renal function when compared with measurements of serum creatinine, urea, cystatin C, and eGFR for detecting early changes in renal function.

This study involved a comparison of the finding in children before surgery (pre-therapy) and after surgery (post-therapy). The concentrations of urine microalbumin, serum IgG, A1M, and NAG in the pre-therapy group were similar to those in the post-therapy group in both boys and girls. These findings indicated that these study parameters were consistent, and were not significantly influenced by surgical correction and drug therapy. Also, these findings indicated that the use of serum and urinary biomarkers of early renal injury for evaluating early changes in renal function was feasible and reliable.

Urinary microalbumin, serum transferrin, and IgG, the molecular weights of which are 65 KD, 77 KD, and 150KD, respectively, are commonly used biomarkers for assessing early changes in renal glomerular filtration function. Urine microalbumin and serum transferrin, with isoelectric points that ranged from between 4.7–5.2, are both negatively charged, low molecular weight (LMW) proteins that are commonly used to detect the selective charge in the barrier function of the glomerular filtration membrane. When the glomerular filtration membrane is damaged by inflammation, metabolic disorders, or immune factors, the selective charge barrier might be destroyed and lead to an increase of the urinary microalbumin and serum transferrin concentrations. However, IgG, an electrically neutral protein, is usually considered to be a sign of membrane mesh selective barrier damage. The findings of the present

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study showed that the concentrations of urine microalbumin and serum transferrin were within normal reference ranges in all patients, which indicated that the selective charge barrier of the glomerular filtration membrane was not injured. There were six patients whose urinary IgG concentration exceeded the normal reference range, which was possibly attributed to membrane mesh selective barrier damage.

There were four patients whose B2M concentration exceeded the normal reference value among the 16 patients with congenital scoliosis and congenital anomalies of the kidney and urinary tract. In healthy children, urinary B2M and urinary A1M had similar excretion and reabsorption processes. However, the statistical results of these findings were not similar, and this discrepancy might be explained by the fact that urinary B2M was not as sensitive as A1M [28,29]. Previous studies have shown that urinary B2M, compared with A1M, was more affected by the urinary pH value and easily degraded at a urinary pH of less than 6.0, and the longer the urine specimen was preserved, the more the B2M became degraded [28,29]. However, in the present study, impairment of urinary A1M reabsorption was an antecedent to the expression of urinary B2M levels, and the concentration of urinary A1M was greater compared with urinary B2M, which was easier to detect by the analyzer. Therefore, urinary A1M was a more sensitive and reliable biomarker than urinary B2M for assessing early renal tubular disease in children with congenital scoliosis and congenital anomalies of the kidney and urinary tract. The superiority of the use of urinary A1M was previously reported to in cadmium-induced tubular dysfunction [30].

NAG is a typical lysosomal enzyme that is predominantly found in the proximal renal tubular cells. The detection of NAG has been reported to be more sensitive than the detection of A1M and B2M for assessing tubular function [31–33]. Acute or chronic damage of renal tubular cells can induce enzyme expression in the lysosomes, the brush-border membrane, and the cytoplasm of cells in the tubular lumen. Increased urinary NAG activity has been described in various disease states, such as heavy metal poisoning and renal disease [31–33]. Also, NAG has been widely accepted as a sensitive marker of impaired renal tubular reabsorption that may contribute to the pathogenesis of increased urinary albumin excretion [34]. In the present study, there was no linear relationship between urine NAG levels and urine microalbumin levels. The pathological link between NAG and urine microalbumin requires further studies with large-scale, multicenter, controlled studies.

The implications of the findings of this study were that all children with congenital scoliosis and congenital anomalies of the kidney and urinary tract were asymptomatic. However, children with congenital anomalies of the kidney and urinary tract are at increased risk of urinary tract infection, stone formation, and obstructive uropathy, and are reported to have a 20-fold infection risk when compared with adults [35].

There are no reliable indicators for predicting whether congenital anomalies of the kidney and urinary tract can progress to end-stage renal disease in clinical practice. Therefore, to better protect the kidney, more attention should be given to long-term monitoring of renal function in children, by both physicians and their families. Physicians should explain the prognosis and avoid using nephrotoxic drugs, such as sulfonamides, and some types of imaging contrast agents. Long-term follow-up, avoiding kidney injury, monitoring for symptoms and timely treatment are necessary and might be key measures to improve clinical outcomes.

This study had several limitations. The study population was small in size, consisting of 16 patients who required surgical correction for congenital anomalies of the kidney and urinary tract, and patients who did not need surgical correction were not included. Therefore, the study population was not representative of the population of patients with congenital scoliosis combined with congenital anomalies of the kidney and urinary tract. The limited number of patients and the fact that the study was performed in a single center were factors that might have affected the results of this study.

Conclusions

The findings of this study showed that routine tests of renal function were normal in children with congenital scoliosis and congenital anomalies of the kidney and urinary tract, but early changes in renal function occurred before surgical treatment, indicating long-term follow-up of renal function is required. To our knowledge, this study was the first to evaluate renal function in children with congenital scoliosis and congenital anomalies of the kidney and urinary tract and our findings concluded that early renal function impairment, especially renal tubular injury, had occurred, and this impairment was not significantly influenced by surgical treatment. To better protect renal function in these patients, long-term follow-up, avoiding kidney injury, early detection of patient symptoms and undergoing timely medical and surgical intervention might be key measures to improve clinical outcomes.

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Conflict of interest

None.

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