

Impact of Chronic Functional Constipation on Lower Urinary Tract System: A Cases – Control Study

Mitra Naseri,¹ Rahil Daghmagh,² Seyed Ali Jafari,³
Hamid Reza Kianifar,³ Seyed Ali Alamdaran,⁴ Elham Bakhtiari,⁵
Matin Daneshmand²

¹Pediatric nephrology department, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

²Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

³Pediatric Gastroenterology Department, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

⁴Pediatric Radiology Department, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

⁵Clinical Research Development Unit, Mashhad University of Medical Sciences, Mashhad, Iran

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Introduction. Association of constipation with incomplete bladder emptying, functional bladder outlet un-coordination, urinary tract infection (UTI), and upper urinary tract dilatation has been reported. We designed a study to determine the impact of chronic functional constipation on kidney and bladder ultrasound parameters, the results of the uroflowmetry test, and its association with UTI.

Methods. The study group consisted of 24 cases and 48 controls, who were children between 5 to 18 years-old, from June 2017 to June 2018. The case group included children with chronic functional constipation. The healthy children with urinary continence and regular bowel habits without any history of UTI were considered as the control group. The variables were bladder volume, post-voiding urinary residual volume, full and empty bladder wall thicknesses, uroflowmetry parameters and, UTI prevalence.

Results. There were no significant differences in the prevalence of UTI, upper urinary tract dilatation on kidney ultrasound, uroflowmetry and, bladder ultrasound parameters between the case and control groups ($P > .05$ for all). We found abnormal uroflowmetry curves in 58.3% and 35.4% of the case and control groups, respectively ($P > .05$) and a higher rate of staccato curves in constipated compared to healthy children.

Conclusion. the prevalence of UTI and upper urinary tract dilatation on kidney ultrasonography are not significantly different between constipated and healthy children. Moreover, it seems that chronic constipation has no significant impact on the storage and emptying functions of the bladder. The higher frequency of staccato curves in constipated compared to healthy children can indicate that fecal mass causes detrusor sphincter dyssynergia.

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INTRODUCTION

Constipation is common among outpatient pediatric patients. It is defined as less than three bowel movements per week, accompanied by hard, dry, small-sized stools with difficult elimination. Prevalence rates of 14% and 4 to 37%

were reported for chronic idiopathic constipation in adults and in children, respectively.^{1,2} Rectum and bladder originate from an embryological origin in the cloaca with identical motor nerve supplies.³ Overactive bladder (OAB), as well as fecal and urinary incontinence, have been found

more frequent in constipated children than those without constipation.^{2,4} Bladder bowel dysfunction (BBD) is a clinical entity characterized by the association of lower urinary tract symptoms (LUTS) with constipation and or encopresis.⁵

In chronic constipation, the compressive effects of loaded stools within the rectum decrease the bladder capacity. This problem results in LUTS such as urgency and frequency, incomplete bladder emptying and, significant post-void residual volumes.⁶

The main aim of this study was to evaluate the impact of chronic functional constipation on kidney and bladder ultrasound parameters, the results of the uroflowmetry test, and its association with urinary tract infection (UTI). LUTS indicates a decreased bladder volume (BV) with symptoms of increased voiding frequency, urgency, urge incontinence, and enuresis. But we emphasized those suggestive of voiding dysfunction like decreased voiding frequency and holding maneuver.

MATERIALS AND METHODS

We conducted a case-control study from June 2017 to June 2018.

Twenty-four pediatric patients (5 to 18 years) with chronic functional constipation were considered as the case group. Chronic functional constipation was defined by Rome III criteria.⁷ These criteria included two or more following criteria in a child ≥ 4 years (without the criteria of irritable bowel syndrome): \leq two weekly defecations, \geq one weekly episode of fecal incontinence, painful or hard bowel movements, obstructing the toilet by large diameter stool, and posturing indicative of stool retention. Forty-eight healthy children referred to the pediatric clinic for minor illnesses such as common cold were considered as the control group if they had all of the following criteria:

- 1) Age matched with the case group (5 to 18 years)
- 2) Having no history of UTI in the past
- 3) Having a regular bowel defecation pattern (painless defecation \geq three times a week and no fecal incontinence)
- 4) Having urinary continence during the day and night
- 5) Having no history of gastrointestinal, urinary tract, central nervous system, or spinal cord surgeries

- 6) Having normal mental status, and physical examination

A nephrologist did the physical examinations of the abdomen and genitalia for any evidence of cutaneous stigmata (e.g., hemangiomas, hairy patches, masses, and tails and midline dimples), abnormal gluteal clefts, short sacrum or sacral agenesis suggestive of spinal dysraphism in the case and control groups. Urine sampling was from mid-stream and, any of growing a single urinary pathogen with a colony-forming unit (CFU /mL) $\geq 10^5$ was considered as positive urine culture and defined as UTI. The demographic characteristics of case and control groups are presented in Table 1. We did urine analysis, culture, kidney and bladder ultrasound and, the simple uroflowmetry test in both groups. First 102 children, 33 cases with chronic functional constipation, and 69 healthy children were enrolled in the study. We excluded those with missing one or more tests and, 72 cases were eligible for analysis. The case group (n = 24) was referred from the pediatric gastrointestinal clinic. The control group (48 cases) was selected from healthy children referred to the pediatric clinics.

Methods of Kidney-bladder Ultrasound Examination

Each individual underwent at least two ultrasound studies. The first ultrasonography on kidney and bladder was done during the maximum need to void and, the second one was done post voiding. An Estate Class C (Italy) or Samsung H60 (Korea) ultrasound with convex probe (frequency 3.5 and 5 MHz) was used. If the first measured post voiding urinary residue (PVURV), i.e. PVURV1 was more than 10 to 15 CC (depending on the age), the child was asked to void again and then the dual-PVURV (PVURV2) was checked. Two coronal and sagittal views of

Table 1. Basic Demographic Characteristics of Case and Control Groups

Variable	Case Group (n = 24) n (%) or mean \pm SD	Control Group (n = 48) n (%) or mean \pm SD	P
Gender			
Girl	15 (62.5)	27 (56.25)	> .05†
Boy	9 (37.5)	21 (43.75)	
Age, mo	120.86 \pm 39.48	132.3 \pm 37.97	> .05‡

†Chi Square Test

‡Independent T-test

the bladder were used for measuring the PVURV. Ultrasound apparatus automatically calculated BV in milliliters by hemi ellipsoid formula (long axis diameter \times anteroposterior diameter \times transverse diameter \times 0.5).

Measurements of bladder wall thickness (BWT) at full and empty conditions were done in the posterior bladder wall with the 5 MHz probe. A probe was located in the supra-pubic region. It measured the sagittal plane and BWT in the detrusor area.

Bladder volume at the maximum need to void was considered as the functional bladder capacity (FBC). Kidneys were checked for hydronephrosis and hydroureter at full and empty bladder conditions. Bladder wall thicknesses of ≤ 3 and ≤ 5 mm at full and empty bladder conditions were defined as normal, respectively.⁸ In children < 7 years old, PVURV1 and PVURV2 ≥ 30 mL and ≥ 20 mL were defined as abnormal, respectively. For children ≥ 7 years old, PVURV1 ≥ 20 mL and PVURV2 and ≥ 10 mL were considered abnormal, respectively.⁹

Bladder function on filling phase was assessed by measurement of BV on the maximum need to void in bladder ultrasound (US) examination and comparison was done with age matched expected bladder capacity (EBC). The emptying function was evaluated by measuring post-void residual urinary volume (PVRUV).

Age expected bladder capacity (ml) was calculated by the formula: $30 + (\text{age in a year}) \times 30$, which reached up to 390 mL after the age of 12 years.¹⁰ Then the ratio of EBC to functional bladder capacity (FBC) was calculated. We defined small bladder capacity if EBC to FBC ratio was less than 0.65, 0.65 to 1.5 in a normal range and, > 1.5 reported as large bladder capacity.¹⁰

Uroflowmetry Study

Uroflowmetry was done as the standard method. The boys voided in sitting or standing positions and girls in sitting positions with adequate foot support.¹¹ Three uroflowmetry tests were done for each individual. Uroflows with voiding volume (VV) < 50 mL were excluded from interpretation. Average flow rate (AFR) (mL/s), maximum flow rate (MFR) (mL/s), time to maximum flow rate (TMFR) (second), VV (mL), and voiding time (VT) (second) were considered for analysis.

We defined five uroflowmetry patterns: bell-

shaped, tower-shaped, plateau-shaped, interrupted-shaped, and staccato curves based on uroflowmetry curves. Bell-shaped curves were considered as normal and the others as abnormal curves.¹¹ Voided volume on uroflowmetry test was an indicator of bladder function in the filling phase. Coordination between detrusor and bladder neck muscles was assessed by the shape of uroflow curves. We did the uroflowmetry test in a cooperative case with sterile urine.

Sample Size

Sample size was calculated as 24 patients in case and 48 subjects in the control group according to infrequent voiding (decreased voiding frequency) in children with and without constipation (0.2 ± 0.6 and 0.7 ± 1.1 , respectively) by Chang *et al.*, (considering $\alpha = 0.5$ and $\beta = 0.2$).¹²

Statistical Analysis

One-Sample t test was used to check the normal distribution of variables, chi-square, independent t test, and if needed non-parametric tests were used for data analysis, and *P* values $< .05$ were considered as a significant difference.

RESULTS

Urinary tract infection was found in 3/24 (12.5%) and 2/48 (4.15%) children in the case and control groups, respectively (*P* $> .05$).

Mild dilatation of the upper urinary tract system was reported in kidney US of 2/24 (8.3%) and 2/48 (4.15%) subjects in case and control groups, respectively (*P* $> .05$). In both constipated children, dilatation of the upper urinary tract system resolved after voiding, one after single and another after double voiding. In one out of two children in the control group, mild dilatation of the upper urinary tract system persisted after voiding. We compared bladder US parameters in age (ranges: < 7 and ≥ 7 years) in both groups (Table 2). We could not find any significant differences in BV, BWT in the full and empty bladder, PVURV1, PVURV2, FBC/EBC between the case and control groups (*P* $> .05$ for all) (Table 2).

Small capacity bladder (FBC/EBC < 0.65) was noted in 11/24 children (45.8%) in case and 25/48 subject (52.08%) in control groups. One patient in case (4.15%) and 4 children (8.33%) in control groups had large capacity bladders (FBC/

Table 2. Bladder Ultrasound Parameters in the Case Compared to Control Group

Variables	Case Group Median (IQR) ¹⁰	Control Group Median (IQR)	P ¹¹
Bladder Volume (BV ¹), cc	168 (121.75, 304.5)	203 (120, 361.75)	> .05
EBC, ² cc	300 (270, 415)	340 (295, 442.5)	> .05
FBC ³ / EBC, cc/cc	0.66 (0.43, 0.75)	0.59 (0.32, 0.87)	> .05
BWT in Full Bladder, ⁴ mm	2 (1.5, 2.37)	1.65 (1.5, 2)	> .05
BWT in Empty Bladder, mm	4 (3, 5)	4 (3, 4.5)	> .05
PVRUV, ⁵ 1 cc	18.5 (5.75, 34.75)	20 (5.5, 42.5)	> .05
PVRUV, ² 6 cc	4.5 (0.75, 15.75)	6.5 (0.37, 10.75)	> .05
Variables	Case Group; (n = 24) n (%)	Control Group; (n = 48) n (%)	P
PVR, ⁷ > 30 mL ⁸	2 (50)	2 (33.3)	> .05 ¹²
PVR ≤ 30 mL	2 (50)	4 (66.4)	
Total Cases	4 (100)	6 (100)	
PVR > 20 mL ⁹	9 (45)	22 (52.4)	> .05 ¹³
PVR ≤ 20 mL	11 (55)	20 (47.6)	
Total Cases	20 (100)	42 (100)	

¹Bladder volume at maximum need to void, ²Expected bladder capacity [age (year) + 1 × 30 (mL)], ³Functional bladder capacity, ⁴Bladder wall thickness, ⁵Single post void residual urine volume, ⁶Dual post void residual urine volume, ⁷Post void residue, ⁸Age group ≤ 7 years (n = 10), including 4 and 6 children in case and control groups; respectively, ⁹Age group > 7 years (n = 62), including 20 and 42 children in case and control groups; respectively, ¹⁰Inter quartile range, ¹¹Mann-Whitney test, ¹²Fisher exact test, ¹³Chi square test

EBC > 1.5). Normal capacity bladder was noted in 50% (n = 12) and 39.6% (n = 19) of case and control groups, respectively ($P > .05$). Single and dual PVURVs were reported as 0 to 100 CC and 0 to 57 CC, in the case and 0 to 156 CC and 0 to 35 CC, in the control group, respectively. Each person performed the uroflowmetry test three times.

The mean of each parameter was calculated and considered in the analysis (Table 3). We found abnormal uroflowmetry curves in 14/24 (58.3%) and 17/48 (35.4%) of children in the case and control groups, respectively ($P > .05$). The most common abnormal uroflowmetry curve was staccato which was reported in 13/24 (54.15%) and 15/48 (31.25%)

of case and control groups, respectively ($P > .05$).

Abnormal LUTS including nocturnal enuresis, daytime wetting, holding maneuvers, urgency, urge incontinence and giggle incontinence were reported in 5 (20.8%), 3 (12.5%), 3 (12.5%), 2 (8.3%), 2 (8.3%), and one (4.15%), with chronic functional constipation, respectively. In the control group, decreased voiding frequency (voiding number ≤ 3 times in a day) was found in 3 (6.25%), holding maneuver and urgency each was reported in 2 (4.15%) children. One child complained about dribbling and straining. Figures 1 and 2 present results of uroflowmetry tests in 2 cases with chronic functional constipation.

Table 3. Uroflowmetry Test Findings in Case Versus Control Group

Variables	Case Group (n = 24) Median (IQR) ¹	Control Group (n = 48) Median (IQR)	P ²
AFR, ³ mL/s	19.03 (14.80, 25.05)	22.43 (17.09, 27.26)	> .05
MFR, ⁴ mL/s	41.21 (29.45, 52.63)	48.18 (36.46, 64.90)	> .05
TMFR, ⁵ Second	7.11 (5.11, 11.35)	7 (5.23, 9.90)	> .05
VV, ⁶ mL	399.35 (267.70, 552.77)	450.56 (350.74, 610.94)	> .05
FT, ⁷ Second	21.08 (13.48, 24.33)	18.43 (12.70, 22.10)	> .05
VT, ⁸ Second	52.06 (32.31, 71.85)	49.31 (35.45, 62.05)	> .05
Variables	Case Group (n = 24) n (%)	Control group (n = 48) n (%)	P ⁹
Staccato curve	13 (54.15)	15 (31.25)	> .05
Non- staccato curves	11 (45.85)	33 (68.75)	
Abnormal uroflowmetry patterns	14 (58.3)	17 (35.4)	> .05
Normal uroflowmetry patterns	10 (41.7)	31 (64.6)	

¹Interquartile Range, ²Mann-Whitney test, ³Average flow rate, ⁴Maximum flow rate, ⁵Time to maximum flow rate, ⁶Voided volume, ⁷Flow time, ⁸Voiding time, ⁹????????????????????

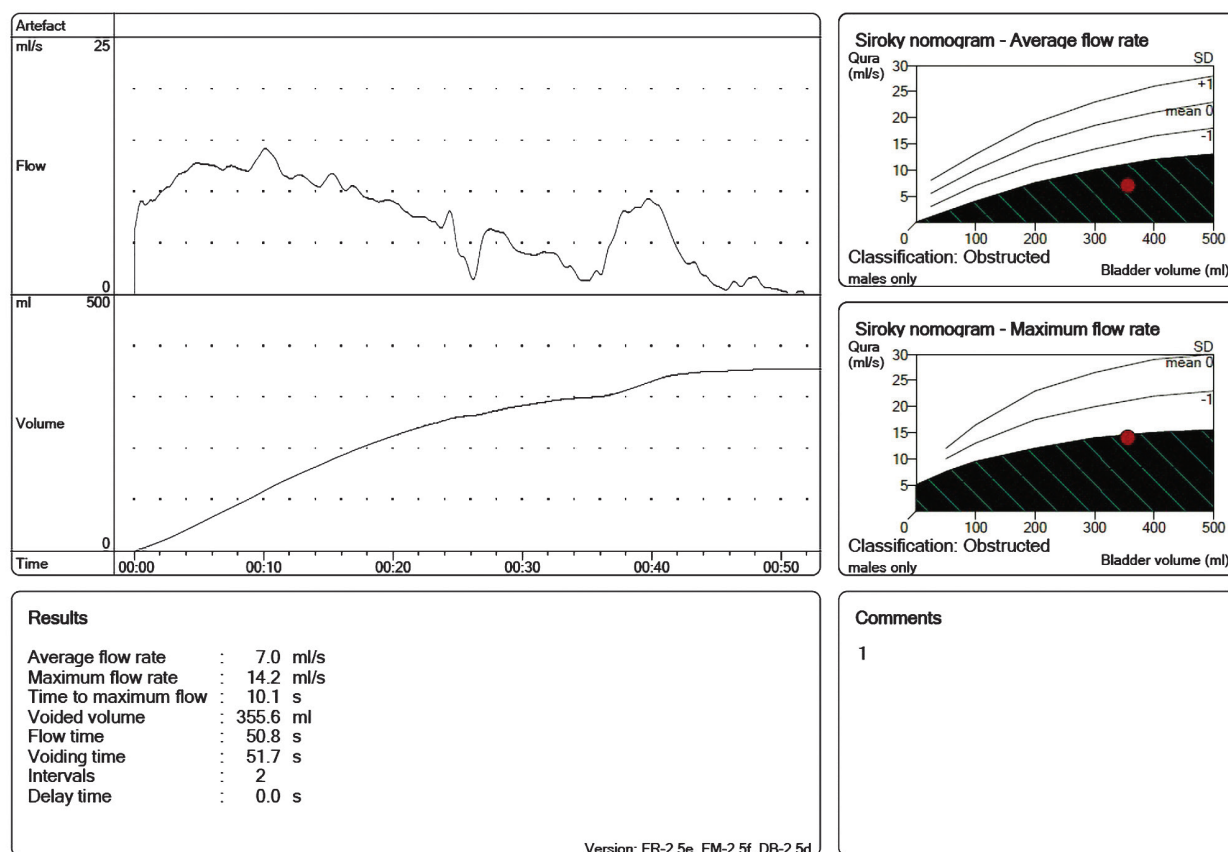


Figure 1. Uroflowmetry of a 14 years old boy in the constipated group. It presents a staccato curve. Bladder volume = 250 cc, expected bladder capacity = 390 cc, and FBC/ EBC (cc/cc) was 0.64 which indicated small bladder capacity. Bladder wall thicknesses at full and empty conditions and single -PVURV were normal (3mm and 5 mm, and 40 cc, respectively). Dual PVURV was 4.5 cc. Renal ultrasound examination was normal. Normal urine analysis and negative urine culture were other findings. There was no history of urinary tract infection in past. He wetted himself during the day.

DISCUSSION

Constipation accounts for 3 to 5% of referral cases to pediatric clinics and up to 25% of outpatient pediatric gastroenterology visits.¹³ An association between chronic constipation with OAB,⁴ enuresis, infrequent voiding, and holding maneuvers have been noted.¹⁴⁻¹⁶ Kasirga *et al.* found that the risk of UTI increases in patients with chronic functional constipation.¹⁷ Sujatha *et al.* reported a frequency of 2% for UTI among 131 children with functional constipation.¹⁸ The frequency of UTI in the current study in constipated children was six times (12.5%) higher than that reported by Sujatha *et al.*

As our series, Sarvari *et al.* revealed no significant difference in the prevalence of UTI between children with chronic functional constipation and the control group (13.3% and 6.7%, respectively; $P > .05$).¹⁹

In healthy children, constipation accompanies incomplete bladder emptying. It is associated with an increased PVRUV with a significant P value

($P < .05$). It is noteworthy that despite incomplete bladder emptying, urgency symptom scores do not increase in constipated children.²⁰

A correlation between chronic constipation and functional bladder outlet discoordination has been reported. In addition, constipation can potentially result in UTI, enuresis, vesicoureteral reflux, and upper renal tract dilatation.²¹ Fecal masses in chronic constipation can compress the ureters and leads to upper urinary tract dilatation and rarely obstructive nephropathy.²² In the current study dilatation of the upper urinary tract system was more frequent in the constipated, compared with the control group (8.3% vs. 4.15%). However, the difference was not significant ($P > .05$).

Measuring the bladder wall thickness is a non-invasive test for the diagnosis of bladder outlet obstruction. Low intra- and inter-observer variabilities for US measurements of the BWT have been reported.²³ The best and most accurate

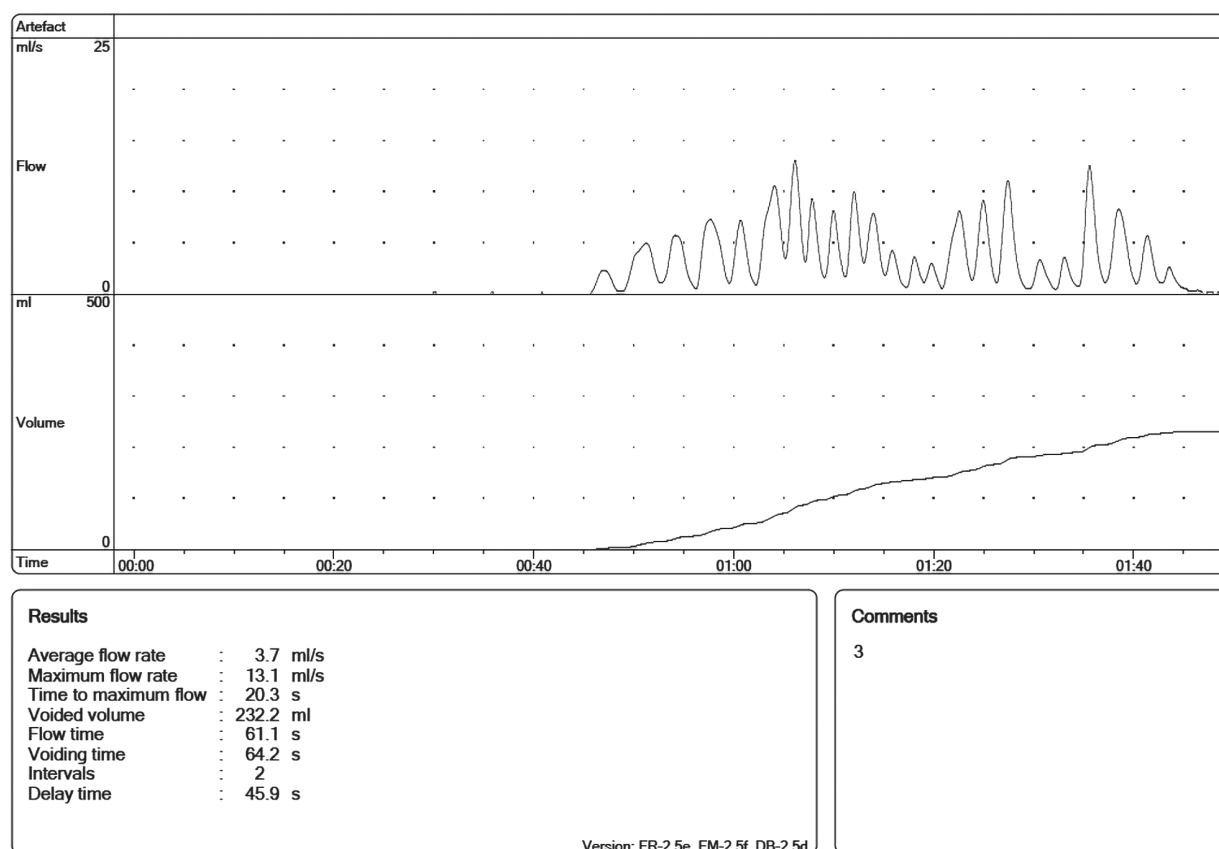


Figure 2. Interrupted shaped uroflow curves in 16 years and 9 months, old girls, with chronic functional constipation. Bladder volume (measured by bladder sonography) = 820 cc, expected bladder capacity = 390 cc, and FBC/ EBC (cc/cc) was 2.1 which indicated large bladder capacity. Bladder wall thicknesses at full and empty conditions and single -PVURV were normal (1 mm and 2 mm, and 3.5 cc; respectively). Renal ultrasound examination was normal. She had no history of urinary tract infection in past. At the time of the study, urinalysis noted white blood cells (WBC) of 18 to 20 in high power field (HPF), and urine culture was positive [E-coli with a colony count $> 10^5$ colony-forming unit (CFU)]. She had urinary control day and night with no abnormal lower urinary symptoms.

time for measuring BV is at the time of maximum need to void and in the full bladder condition and empty bladder for BWT.²⁴

Evaluation of BWT during voiding shows a higher measurement compared to the results of before or after voiding. When the patient has a maximum voiding urgency, FBC should be measured.²⁵ Rowe *et al.* found a high correlation between the BV measured by the US with the volume obtained by bladder catheterization in pediatrics.²⁶

The Koff formula is a different formula that is used for the measurement of bladder capacity by age. It has been established as the gold standard in the literature.²⁷

Currently, Seibold *et al.* used a different formula $[(\text{Age} \times 30) / 2]$, and believe that it can accurately determine bladder capacity in healthy children.²⁸

New experiments in animal models suggest detrusor overactivity in constipated models that

contribute to the development of decreased bladder capacity and BBD.²⁹ Bladder volume at the time of maximum need to void is an indicator of FBC and presents bladder function in the filling phase. In the current study, BV was not significantly different in case vs. control groups (233.91 ± 169.36 mL vs. 43.22 ± 168.87 mL, respectively; $P > .05$). We found a Urinary residual volume ≥ 1 CC after single voiding in 23/24 (95.8%) and 44/48 (91.6%) children in case and control groups, respectively ($P > .05$). After dual-voiding, there was a residual urine volume ≥ 1 CC in 17/22 (77.3%) of cases and 34/42 (81%) of control groups ($P > .05$). We noted daytime urinary incontinence and enuresis in 12.5% and 20.8% of children with chronic functional constipation, respectively. The most valuable parameters in the uroflowmetry test interpretation are voided volume, PFR or Q max and, Uroflow curves.¹¹ Peak flow rate is the most

reliable parameter for assessing bladder outflow. Bell-shaped curves (normal uroflowmetry curves) have been reported in 97.2% of Swedish, 90% of Spanish, and 63% of Chinese children, respectively.³⁰⁻³² In the current study, the prevalence of bell-shaped curves in healthy children (control group) was 64.5%, which was near to that reported in Chinese children (63%).

The main tools for measurement of the maximum VV are frequency volume chart, bladder ultrasound and, the uroflowmetry test. That is indicative of FBC. In the uroflowmetry study, VV + urinary residue represents FBC. The largest voided volume, in a bladder diary, also indicates FBC.¹⁰

Abnormal curves in uroflow are indicative of altered bladder physiology. Tower-shaped curves are seen in bladder sphincter hyperactivity, interrupted curves indicate the detrusor low-activity, plateau curves suggest anatomical bladder outflow obstruction, and finally, staccato curves represent detrusor sphincter dyssynergia.¹¹ Abnormal uroflowmetry curves were found in 58.3% of the case group and 35.4% of the control group ($P = 0.064$). In addition, staccato curves were noted in 54.15% and 31.25% of case and control groups, respectively ($P = 0.06$). The higher frequency of staccato curves in the case group in comparison to the control group suggests bladder outlet discoordination in patients with functional constipation. The discoordination between detrusor and sphincter muscles in the voiding phase may be due to the compressive effects of fecal masses on the bladder. The clinical impact of detrusor-sphincter dyssynergia (DSD) increased PVURV. The single and dual PVURVs were compared between children with the staccato curves in uroflowmetry tests vs. those with other uroflow curves. The Children with staccato curves had single and dual PVURVs of 33.26 ± 30.97 mL, and 9.35 ± 11.27 mL, respectively. In the children with the other uroflow curves, the measured single & dual PVURVs were 26.78 ± 38.84 mL and 9.38 ± 11.7 mL, respectively ($P > .05$ for both). There were no significant differences in PVURV1 and PVURV2 among constipated and non-constipated cases ($P > .05$ for both).

A bladder capacity (VV + PVRUV) $> 115\%$ or VV $> 100\%$ of EBC associates with abnormal uroflow patterns and elevated PVRUVs.³³ In our series, of 45 subjects aged ≤ 12 years old (16 patients with

chronic functional constipation and 29 children in the control group), 25 (55.6%) and 20 (44.4%) patients had normal and abnormal uroflowmetry tests, respectively. Two of 4 cases (50%) with a VV $\geq 100\%$ of EBC and 18/41 (43.9%) subjects with a VV $< 100\%$ of EBC, had abnormal uroflow ($P > .05$).

LIMITATIONS OF THE STUDY

Lack of a frequency volume chart was the main limitation of our study.

CONCLUSION

We found that BV and PVRUV, parameters indicative of storage and emptying functions of the bladder, and BWT that represents intravesical pressure are not affected by chronic constipation. In addition, the prevalence of UTI is not significantly higher in constipated compared with healthy children. A Higher frequency of staccato curves on the uroflowmetry test in constipated compared with healthy children may suggest DSD in constipated children. Future studies focusing on the results of uroflowmetry tests, especially uroflow curves before and after treatment of constipation can be attractive.

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Conflict of Interest / Competing Interests

The authors declare no conflict of interest.

Ethical Approval

The ethics committee of Mashhad University of Medical Sciences approved this study.

Consent to Participate

The written consent was obtained from patients or their parents.

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Correspondence to:
 Mitra Naseri, MD
 Pediatric Nephrology Department, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
 Mail Address: Dr. Sheikh Children's Hospital, Naderi Avenue, Taabodi Street, Mashhad, Iran
 Tel: 0098 513 726 9021-25
 Fax: 0098 513 727 3943
 Cellphone: 0098 915 114 1639
 E-mail: Naserim@ mums.ac.ir

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